

# Dietary Supplements in the Perinatal Period

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The physiologic changes of pregnancy, in addition to the nutritional needs of the growing fetus, require supplementation and dietary changes during pregnancy. Additional macronutrient needs include protein and polyunsaturated fatty acids. Micronutrients also have important roles in supporting maternal health and fetal development, including vitamins A, D, C, B<sub>6</sub>, B<sub>12</sub>, and K, in addition to iodine, iron, choline, zinc, calcium, and folate. The most common form of supplementation in pregnancy is oral prenatal vitamins, although these can vary in their composition and inclusion of certain micronutrients. Nutrient supplementation also varies according to pre-pregnancy medical conditions and diagnoses made during pregnancy. Examples of some conditions that require modified supplementation include anemia, multiple gestation, history of bariatric or gastrointestinal surgery, and a personal history or pregnancy history of neural tube defects. Finally, significant socioeconomic drivers of health shape access to adequate pre-pregnancy and perinatal nutrition, and targeted interventions, including supplementation, may be necessary to address these disparities.

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In pregnancy, the needs of the growing fetus and the changes in maternal physiology often require additional supplements and dietary changes. In this article, we aim to review metabolic demands and nutrient requirements in pregnancy, summarize components of dietary supplements, and provide guidance on special populations who require additional or unique dietary supplements in the perinatal period.

Daily caloric requirements are an additional 300 kcal/d, averaged over the entire pregnancy, which accounts for the metabolic activity of maternal tissue and the growth of the fetus and placenta.<sup>1,2</sup> This increased energy requirement is not evenly distributed throughout the span of pregnancy and varies according to the person's prepregnancy weight and

physical activity levels. There is no need for additional energy supplementation in the first trimester, but an additional 340 kcal/d and 452 kcal/d are needed in the second and third trimesters, respectively.<sup>1,2</sup>

## MACRONUTRIENTS

Nutrient requirements in pregnancy can be categorized into macronutrients (carbohydrates, protein, fat) and micronutrients (vitamins, minerals). The recommendation for carbohydrates (45–65% of total calories or at least 175 g) and fat (20–35% of calories, 40–60 g daily) is similar for pregnant and nonpregnant people, but pregnant people need more protein, 71 g/d, compared with the recommended 46 g/d for nonpregnant adult females.<sup>1</sup>

Essential lipids, which cannot be synthesized by the body and must come from nutrition or supplementation, are important for energy storage and cell membrane regulation in the brain and retina.<sup>3</sup> These include long-chain omega-3 polyunsaturated fatty acids (PUFAs), among which the most biologically active omega-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid.<sup>3</sup> Docosahexaenoic acid is important in fetal growth and development.<sup>3</sup> The U.S. Food and Drug Administration recommends supplementation of PUFAs in pregnancy, which is typically 200–300 mg/d docosahexaenoic acid.<sup>4</sup>

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Polyunsaturated fatty acids can be obtained through supplements or by consuming 8–12 ounces of fish per week; other notable sources include flax, hemp, and walnuts. Pregnant people should avoid fish with high mercury concentration, which includes king mackerel, tilefish, shark, swordfish, marlin, orange roughy, and bigeye tuna; canned light tuna, canned albacore or white tuna, and yellowfin tuna are safe to consume in pregnancy.<sup>4</sup> A study of reproductive-aged and pregnant people in the United States reported a mean seafood intake of only 0.44 ounces per day, and 100% consumed less than 8 ounces per day.<sup>5</sup> Observational studies of pregnant people consuming seafood with docosahexaenoic acid suggest improved infant health and neurodevelopmental outcomes with higher consumption of seafood.<sup>6</sup> However, randomized controlled trials of supplements in pregnancy have shown mixed outcomes.<sup>6–8</sup> Helland et al<sup>7</sup> reported higher mental processing scores (a measure of intelligence) at 4 years among children of mothers who took cod liver oil (1,183 mg docosahexaenoic acid, 803 mg eicosapentaenoic acid) compared with corn oil (4,747 mg linoleic acid and 92 mg  $\alpha$ -linolenic acid). In another longitudinal study, mean cognitive and language scores at 18 months and assessments of cognition, language, and executive function at 4 years were not different in pregnant people who received fish oil supplements (800 mg docosahexaenoic acid, 100 mg eicosapentaenoic acid) compared with those who received placebo.<sup>6–8</sup> A systematic review of 9 randomized controlled trials of PUFA supplements in pregnant people concluded that there were no sustained benefits to infant cognition or visual development.<sup>9</sup> The Agency for Healthcare Research and Quality report summarized 95 randomized controlled trials and 48 other prospective longitudinal studies and nested case-control studies of either fish oil supplements or combinations of docosahexaenoic acid and eicosapentaenoic acid in pregnant or breastfeeding people and found no consistent effects on infant health outcomes.<sup>10</sup> Given the available evidence, we typically recommend consumption of fish to achieve the recommended amount of PUFA in pregnancy. Supplementation with docosahexaenoic acid or docosahexaenoic acid in combination with eicosapentaenoic acid is recommended if people do not have access to or have intolerance of fish sources, although the evidence to support this supplementation is limited.

## MICRONUTRIENTS

Several micronutrients have important roles in supporting maternal health and fetal development, and

deficiencies and excesses can have significant clinical implications. Table 1 includes the dietary reference intakes for micronutrients in pregnancy, the majority of which are compiled by Landon et al.<sup>1</sup> In this section, we describe important considerations in supplementation of these nutrients.

- Vitamin A is recommended at 770 micrograms/d in pregnancy. It is important for fetal cardiac and craniofacial development, can cause cranial neural crest cell dysfunction at higher doses, and increases the risk for fetal microcephaly.<sup>1</sup> As a result, this vitamin should be obtained primarily through diet, and high-dose supplements including retinol forms should be avoided. Vitamin A can be found in carrots, leafy green vegetables, and sweet potatoes.<sup>11</sup>
- Vitamin D is recommended at 600 international units/d in pregnancy. Higher-dose regimens used to treat vitamin D deficiency have not been studied during pregnancy, and the optimal serum level for pregnancy is not known, but most experts agree that 1,000–2,000 international units/d of vitamin D is safe.<sup>12</sup> Notably, several population studies, including people from the United States, found that 40–50% of pregnant people were deficient in vitamin D despite supplement use.<sup>13,14</sup> Vitamin D is a fat-soluble vitamin, and deficiency can be secondary to malabsorption. Vitamin D can be found in fortified milk and wheat products, salmon, mackerel, fish liver oils, and egg yolks.<sup>11</sup>
- Vitamin C is recommended at 75 mg/d in pregnancy. The majority of people receive adequate amounts through diet, but supplements may be particularly important for people who smoke cigarettes as a mediator to reduce oxidative stress. Newborns of pregnant smokers who received 500 mg/d of vitamin C supplements had improved pulmonary function tests and decreased wheezing through the first year of life compared with those who received a placebo.<sup>15</sup> Vitamin C can be found in citrus fruits, strawberries, broccoli, and tomatoes.<sup>11</sup> Emerging literature exists on the association of vitamin C deficiency and preeclampsia, which is discussed later.<sup>16</sup> At this time, insufficient literature exists to recommend vitamin C supplementation specifically for preeclampsia risk reduction.
- Vitamin B<sub>6</sub> supports heme synthesis<sup>1</sup> and is effective for managing nausea and vomiting in pregnancy. It is typically obtained through diet rather than supplements. The American College of Obstetricians & Gynecologists (ACOG) recommends 10–25 mg three times daily for the management of nausea and vomiting in pregnancy, although this amount is more than the daily intake needed to support

**Table 1. Dietary Reference Intake of Micronutrients for Pregnant and Nonpregnant People and Associated Maternal–Fetal Outcomes**

Micronutrient	Proposed Maternal–Fetal Benefit	Potential Risks of Insufficiency
Vitamin A	Fetal craniofacial development <sup>1</sup>	Fetal microcephaly, fetal cardiac defects, increased risk of fetal and maternal infection with excessive amounts, maternal night blindness <sup>1</sup>
Vitamin D	Fetal skeletal development, <sup>1</sup> regulation of fetal angiogenesis, maternal calcium absorption	Reduced fetal long-bone growth, congenital rickets, neonatal fractures <sup>1</sup>
Vitamin C	Antioxidant, fetal pulmonary function <sup>1,15</sup>	Associated with risk of preeclampsia <sup>72</sup>
Vitamin B <sub>6</sub>	Fetal heme synthesis <sup>1</sup>	Associated with risk of preeclampsia, hyperemesis gravidarum, concurrent B <sub>12</sub> and folate deficiency, and neurologic disorders in infants <sup>72</sup>
Vitamin B <sub>12</sub>	Fetal neurodevelopment <sup>19</sup>	Cause of maternal macrocytic anemia, observational studies link vitamin B <sub>12</sub> deficiency to impaired fetal cognitive development <sup>19</sup>
Vitamin K	Maternal and fetal clotting factor synthesis <sup>1</sup>	Risk of maternal hemorrhage or neonatal hemorrhage <sup>75</sup>
Iodine	Fetal neurodevelopment <sup>20</sup>	Maternal goiter, maternal hypothyroidism, severe fetal hypothyroidism leading to cognitive delay or myxedema <sup>76</sup>
Iron	Prevents maternal anemia; supports fetal growth <sup>1</sup>	Maternal iron-deficiency anemia; subsequently increases risk of maternal and neonatal death, preterm delivery, and low birth weight <sup>1</sup>
Choline	Fetal brain development; fetal neural tube closure <sup>1</sup>	Some association with fetal cognitive and neurobehavioral outcomes (primarily in animal models) <sup>78</sup>
Zinc	Maternal enzyme function; immune support <sup>1</sup>	Intrauterine growth restriction, teratogenesis, fetal demise <sup>1</sup>
Calcium	Fetal skeletal development <sup>1</sup>	Associated with gestational hypertension, preterm delivery, and preeclampsia <sup>1</sup>
Folate	Fetal cell growth; fetal neural tube closure (18–28 d after fertilization) <sup>1</sup>	Fetal neural tube defects, <sup>22,23</sup> maternal anemia

Micronutrient	DRI <sup>1</sup>		Tolerable Upper Intake Level	Populations at Risk of Deficiency
	Nonpregnant	Pregnant		
Vitamin A	700 micrograms/d	770 micrograms/d	3,000 micrograms/d	Malabsorptive disorders (celiac disease, inflammatory bowel disease), chronic liver disease, pancreatic insufficiency
Vitamin D	600 international units/d	600 international units/d; those with prior deficiency may require 1,000–4,000 international units/d	More than 4,000 international units/d	Malabsorptive disorders (celiac disease, inflammatory bowel disease), inadequate sunlight exposure <sup>71</sup>
Vitamin C	75 mg/d	85 mg/d	2,000 mg/d	Alcohol use disorder, history of smoking, type 1 diabetes, malabsorptive disorders (celiac disease, inflammatory bowel disease) <sup>73</sup>
Vitamin B <sub>6</sub>	1.3 mg/d	1.9 mg/d	100 mg/d	Malabsorptive disorders (celiac disease, inflammatory bowel disease), autoimmune diseases (including rheumatoid arthritis), chronic renal disease, isoniazid use <sup>74</sup>
Vitamin B <sub>12</sub>	2.4 micrograms/d	2.6 micrograms/d	Unknown	Pernicious anemia, malabsorptive disorders (celiac disease, inflammatory bowel disease), vegetarian or vegan diet
Vitamin K	90 micrograms/d	90 micrograms/d	Unknown	Malabsorptive disorders (celiac disease, inflammatory bowel disease)
Iodine	150 micrograms/d	250–300 micrograms/d	1,100 micrograms/d	Lactose intolerance or diets without dairy products, <sup>77</sup> diets lacking iodized salt

(continued)

**Table 1. Dietary Reference Intake of Micronutrients for Pregnant and Nonpregnant People and Associated Maternal–Fetal Outcomes (continued)**

Micronutrient	DRI <sup>1</sup>		Tolerable Upper Intake Level	Populations at Risk of Deficiency
	Nonpregnant	Pregnant		
Iron	18 mg/d	27 mg/d	Unknown	Vegetarian or vegan diet, history of heavy menstrual bleeding, malabsorptive disorders (celiac disease, inflammatory bowel disease), multiple gestation
Choline	Approximately 425 mg/d	450 mg/d (550 mg/d breastfeeding)	3,500 mg/d <sup>79</sup>	Concurrent folate or B <sub>12</sub> deficiency
Zinc	8 mg/d	11 mg/d	40 mg	Concurrent use of high-dose iron (more than 60 mg/d) increases risk of zinc deficiency resulting from competitive absorption <sup>22,23</sup>
Calcium	1,000 mg/d (more than 19 y of age)	1,000–1,300 mg/d	2,500 mg/d <sup>80</sup>	Lactose intolerance or diets without dairy products
Folate	400 micrograms/d	400–800 micrograms/d	Unknown	Malabsorptive disorders (celiac disease, inflammatory bowel disease), megaloblastic anemia, alcohol use disorder

DRI, dietary reference intake.

pregnancy (1.9 mg/d) in the absence of these symptoms.<sup>17</sup> Foods high in B vitamins include liver, pork, chicken, bananas, beans, and whole-grain breads.<sup>11</sup>

- Vitamin B<sub>12</sub> is associated with fetal brain growth, myelination, neurogenesis, and synaptic connectivity, although this evidence is limited and found primarily in observational studies.<sup>18</sup> The recommended intake in pregnancy is 2.6 micrograms/d. Separately, vitamin B<sub>12</sub> deficiency is a known cause of maternal anemia and may also be associated with maternal metabolic dysfunction and insulin resistance.<sup>19</sup>
- Vitamin K is essential for clotting factor synthesis, but poor placental transfer in all pregnancies necessitates neonatal supplementation.<sup>1</sup> The recommended dietary intake is 90 micrograms/d, which is typically obtained through diet. Common dietary sources include spinach, kale, broccoli, iceberg lettuce, and fats and oils, including soybean and canola oil.<sup>11</sup>
- Iodine requirements in pregnancy are 250–300 micrograms/d. Iodine deficiency has been identified by the World Health Organization as the leading preventable cause of childhood developmental delay and is a leading cause of fetal hypothyroidism.<sup>20</sup> This association is well described in the literature, although most people obtain sufficient iodine through fortified diets including iodized salt.

- Iron is a mineral used in red blood cells. Iron requirements increase in pregnancy to support increased maternal blood volume and fetal demands.<sup>1</sup> In pregnancy, the recommended daily intake of iron is 27 mg/d. Iron supplements for preexisting anemia are discussed separately within this article. Iron deficiency is a well-known cause of maternal anemia and has lasting maternal cardiovascular effects. Iron supplementation should be considered a priority in pregnancy. Iron can be found in beans, lentils, enriched wheat products, beef, turkey, liver, and shrimp.<sup>11</sup> Iron absorption is aided by foods rich in vitamin C, including oranges, grapefruit, strawberries, and peppers.<sup>11</sup>
- Choline is recommended at 450 mg/d and 550 mg/d in lactating people. Choline supports fetal brain development and is found in foods such as eggs, peanuts, chicken, beef, and soy products.<sup>1</sup> Although this topic is the subject of ongoing research, particularly in the setting of prenatal alcohol exposure, very limited evidence suggests that choline supplements are associated with improved fetal cognitive outcomes in the broader population.<sup>21</sup> There is no robust evidence to support additional choline supplements in pregnancy, although choline is commonly found in prenatal supplements.
- Zinc is recommended at 11 mg/d in pregnancy. Although routine supplementation is likely not needed, pregnant people may require zinc supplements when high-dose iron (more than 60 mg/d) is

administered because of competitive absorption.<sup>22,23</sup>

- Calcium is recommended at 1,000–1,300 mg/d in pregnancy. This nutrient is available through dairy products, but supplements may be needed in those with vegan diets or in people with lactose intolerance. Calcium is also found in broccoli, fortified wheat products, almonds, sesame seeds, sardines, and dark leafy green vegetables.<sup>11</sup> Calcium is essential for fetal skeletal development.<sup>1</sup>
- Folate is critical for neural tube closure, which is completed by 28 days after fertilization, emphasizing the need for sufficient intake before 6 weeks of gestation. The Centers for Disease Control and Prevention recommends that all people with the potential to be pregnant consume 400 micrograms/d of folic acid.<sup>22,23</sup> Folate is the formulation found naturally in foods, whereas folic acid is the synthetic form used in supplements and fortified foods.<sup>11</sup> Because humans cannot synthesize folate, dietary or supplemental intake is essential, making it the most prevalent micronutrient deficiency in pregnancy.

There is no indication for routine screening for micronutrient deficiencies or excesses in the absence of a known deficiency, symptoms of a deficiency, or prior bariatric surgery. However, included in Table 1 are the conditions or known risk factors for deficiency. We recommend that clinicians review their patients' history for these risk factors to determine the need for additional supplementation or discussion of diet modification.

## PRENATAL VITAMINS

Prenatal vitamins contain both vitamins and micronutrients and are a form of a multivitamin or multi-nutrient supplement that is specially designed for people planning a pregnancy or pregnant people. For purposes of this article, the term “prenatal vitamin” will be used to refer to these multivitamin supplements. Prenatal vitamins emerged as a key component of prenatal care in the mid-20th century after the discovery of the role of folic acid in preventing neural tube defects.<sup>24</sup> Subsequent public health efforts in the United States and internationally such as the 1998 Folate Fortification Program mandated the enrichment of cereals, pastas, rice, and breads with folate, resulting in a marked decline in neural tube defect prevalence.<sup>24</sup> These interventions were replicated with similar success in Canada.<sup>25</sup>

Prenatal vitamins are formulated to provide a range of micronutrients critical for pregnancy but do not contain all the recommended micronutrients. Folic acid remains foundational, with most commer-

cially available prenatal vitamins containing 800 micrograms, although specialized prenatal vitamins may contain more folic acid.<sup>26</sup>

Iron, typically included as either ferrous fumarate or polysaccharide iron complex, can be found at doses of 18–27 mg in most prenatal vitamins.<sup>27,28</sup> Of note, the amount of iron can differ according to the formulation, with tablets or soft gels typically containing iron, whereas gummy prenatal vitamins do not contain iron. The amount of elemental iron, which refers to nutritionally available iron, differs according to the specific form of iron included. For example, ferrous fumarate is 33% elemental iron, which means that 300 mg ferrous fumarate includes only about 99 mg elemental iron.<sup>29</sup> We recommend that clinicians be attentive to the type of prenatal vitamins their patients are taking and the amount of iron the supplements contain, especially if they are diagnosed with concurrent iron deficiency.

Calcium is not always included in prenatal vitamins<sup>28</sup>; if it is included, the amount ranges from 150 to 300 mg/tablet.<sup>27,30</sup> Calcium can interfere with iron metabolism; subsequently, clinicians may prescribe calcium supplements separately so that they can be taken at a different time of day from an iron-containing prenatal vitamin. Other vitamins typically included in prenatal vitamins are vitamin D (commonly 600 international units but up to 2000 international units in some brands), vitamin C (commonly 85 mg), and vitamin B<sub>12</sub> (commonly 2.8 micrograms, although some brands offer up to 8 micrograms).<sup>27,28,30</sup> Essential elements such as iodine (150 micrograms) and zinc (13 mg), as well as PUFAs such as docosahexaenoic acid (200–350 mg), are also frequently included.<sup>27,28</sup>

Prenatal vitamins are regulated by the U.S. Food and Drug Administration as dietary supplements after they are on the market. Dietary supplements must comply with the Dietary Supplement Health and Education Act of 1994.<sup>31</sup> A *supplement* is defined as “any product which contains one or more dietary ingredients, such as vitamins, minerals, herbs or other botanicals, or amino acids, used to supplement the diet.”<sup>31</sup> However, there are no specific mandated ingredients in a prenatal vitamin, and the U.S. Food and Drug Administration does not regulate their effectiveness. Notably, a recent analysis of 48 top-selling prenatal vitamins found that none of them met ACOG's recommendations for five key nutrients: folic acid, iron, docosahexaenoic acid, vitamin D, and calcium.<sup>32</sup> The Government Accountability Office has called for increased regulation of prenatal vitamins, given the inconsistencies

in labeling and differences between what is in supplements and what is recommended.<sup>33</sup>

Appendix 1, available online at <http://links.lww.com/AOG/E386>, provides examples of micronutrient contents and doses in three prenatal vitamins with omega-3 PUFAs that are available over-the-counter in the United States and commonly taken during pregnancy. Two of the supplements were chosen because of their high status on the current market share. We do not recommend a particular brand of prenatal vitamins. Instead, it is important to focus on taking a supplement that contains at least 400 micrograms folic acid and 27 mg iron, which are found in all three example vitamins in Appendix 1, <http://links.lww.com/AOG/E386>. Of note, the composition of these vitamins is generally similar, but they do not contain the same micronutrients or doses.

The other important aspect of prenatal vitamin supplements is that they are taken consistently. A prenatal vitamin should not be the only source of micronutrients; a balanced diet is essential to complete nutrition during pregnancy. If people are not consuming diets that include fish, we also recommend a prenatal vitamin or an additional supplement containing at least 200 mg docosahexaenoic acid or docosahexaenoic acid combined with eicosapentaenoic acid. Vitamin C, vitamin D, calcium, iodine, choline, and zinc may be included in prenatal vitamins but are not essential if pregnant people are consuming a balanced diet.

## PREPREGNANCY AND PREGNANCY SUPPLEMENTS

People with the potential to be pregnant should take a prenatal vitamin at least 1 month, but ideally 2–3 months, before becoming pregnant.<sup>20,34</sup> This recommendation should be included as part of routine prepregnancy counseling. Prenatal vitamin supplements can cease at delivery for most people, but some experts recommend continuing supplements for at least 4–6 weeks postpartum.<sup>20</sup> For some pregnant people, a prenatal vitamin may not be necessary. For example, people without comorbidities or who consistently consume a balanced diet may not require all the components in a prenatal vitamin. However, given that most people in the United States do not meet the recommendations for nutrition during pregnancy and given the appetite changes and food aversions that commonly accompany pregnancy, it may be difficult to obtain the critical micronutrients (eg, folate, iron) from diet alone. Furthermore, a large systematic review of 17 trials reported that a daily multiple micronu-

trient supplement containing iron and folic acid compared with individual supplements of iron and folic acid reduced the risk for small-for-gestational-age birth weight (average risk reduction 0.92, 95% CI, 0.88–0.97) in low- and middle-income countries.<sup>35</sup> It is our practice to either recommend or prescribe a prenatal vitamin to all our patients. Pregnant people have hundreds of options for brand or generic formulations with wide variation in costs. We also individually review the content of a patient's prenatal vitamin or other supplements they are taking to ensure that there are no deficits or excesses in supplement consumption.

## DISPARITIES IN NUTRITIONAL STATUS IN PREGNANCY AND PRENATAL VITAMIN USE

There are significant racial and socioeconomic disparities in micronutrient deficiencies, in addition to the use of prenatal vitamins and other supplements in the perinatal period.

Nulliparous pregnant people living in *food deserts* (defined as specific geographic locations lacking consistent, sustainable access to food that is both nutritionally adequate and safe) were more likely to have lower prepregnancy diet quality at baseline, as defined by scores from the Healthy Eating Index, compared with those not living in food deserts.<sup>36</sup> In particular, those living in food deserts were more likely to not meet the five Healthy Eating Index goals for intake of fruit, total vegetables, greens and beans, seafood and plant protein, and fatty acids.<sup>36</sup> As noted previously, these food groups make up the majority of essential pregnancy macronutrients and micronutrients.

National programs intended to provide dietary education and increase access to healthy food such as the Special Supplemental Nutrition Program for Women, Infants, and Children have been shown to improve dietary quality in pregnant people with household incomes less than \$75,000 who use the Special Supplemental Nutrition Program for Women, Infants, and Children compared with nonrecipients.<sup>37</sup> In a large cross-sectional study of 1,314 pregnant people, prenatal vitamin use and use of any supplement were directly correlated with increasing income ( $P<.001$ ); 49.7% of those with a family income-to-poverty ratio below 130% used prenatal supplements compared with 78.4% of those family income-to-poverty ratio above 350%.<sup>38</sup> Prenatal vitamins and dietary supplements vary widely in cost, which results in a financial barrier to access. Although many health insurance products provide coverage for some formulations of prenatal vitamins, underinsured or

uninsured pregnant people or those without access to a prescriber may have to pay out-of-pocket costs.

Racial disparities are known to exist in dietary nutrient intake in addition to the use of dietary supplements. One study examining the burden of nutrition deficiencies among reproductive-aged women in the United States reported that Hispanic and African American women had higher prevalences of multiple micronutrient inadequacies compared with White women, with significant inadequacies in vitamin E, magnesium, iron, and vitamin D.<sup>39</sup> Groth et al<sup>40</sup> found that, among 93 pregnant African American people receiving prenatal care in an urban setting in the United States, estimated average requirements were below the recommendations for folate (66%), vitamin D (100%), and iron (89%) for the entire pregnancy, as measured from 24-hour diet recalls. A combination of 15 observational cohort studies from the U.S. Environmental Influences on Child Health Outcomes Consortium evaluated dietary intake with either 24-hour diet recalls or food frequency questionnaires in pregnant people.<sup>41</sup> The highest risks for inadequate micronutrient intake were found with younger age (specifically between 14 and 18 years of age), non-White race or Hispanic ethnicity, less than a high school education, and obesity. In one study, the use of prenatal vitamins did not differ by race,<sup>42</sup> but another study that measured pill count adherence to supplements found higher adherence among non-Hispanic White (79%) compared with non-Hispanic Black (72%) people, although it is difficult to ascertain whether this was a clinically significant difference.<sup>43</sup> These differences merit further study and highlight inequities in maternal nutrition and micronutrients, which may be a result of varied access.<sup>44</sup> Because there is an ongoing crisis of Black maternal morbidity within the United States,<sup>45</sup> targeted interventions to address disparities within perinatal nutrition are important to investigate.

There is limited research on the use of validated nutrition screening tools in pregnancy. One tool, the International Federation of Gynecology and Obstetrics Nutrition Checklist, has been proposed for use in pregnancy. This tool screens people based on their reported nutritional intake and has country-specific recommendations for supplements.<sup>46</sup> However, this tool and others are limited because they exclude other socioeconomic drivers of health, including economic stability, health literacy and education, and social and community context. It is unclear which particular factors are highly associated with nutritional deficiencies to a degree that would warrant nutritional supplementation or additional screening based on the presence

of these factors alone. We recommend that prenatal care clinicians consider their patients' social drivers of health and diet when prescribing prenatal vitamins and supplements and routinely evaluate their patients' use of recommended supplements. We routinely screen for social drivers of health with an institution-specific tool that enquires about difficulties getting medicines or paying for medicine and food insecurity, among other items. Clinicians use the responses from this screening to tailor individual conversations with patients about nutrition and supplements.

## SPECIAL CONSIDERATIONS FOR NUTRIENT SUPPLEMENTATION

Conditions requiring additional screening or supplementation are listed in Table 2 and described in more detail below. This is not intended to be an exhaustive list but rather describes more commonly encountered conditions in obstetric practice.

### History of Metabolic and Bariatric Surgery

People with a history of bariatric surgery or surgeries that have altered portions of the stomach or intestines are at increased risk for deficiencies in both macronutrients and micronutrients.<sup>2</sup> These deficiencies occur most commonly after malabsorptive procedures such as Roux-en-Y gastric bypass and biliopancreatic diversion, although they are also observed after restrictive procedures such as gastric banding and sleeve gastrectomy.<sup>2</sup> The evaluation and management of macronutrient and micronutrient deficiencies have not been tested for pregnant people after bariatric surgery, so we follow the guidelines of Mechanick et al,<sup>47</sup> which are supported by several national societies for people after metabolic and bariatric surgery. The evaluation includes annual vitamin B<sub>12</sub> levels for all people regardless of the bariatric surgery type and folic acid, iron studies, and vitamin D levels for individuals with Roux-en-Y gastric bypass and biliopancreatic diversion procedures. Given the high prevalence of iron deficiency in pregnancy and its high prevalence after bariatric surgery (18% for gastric sleeve, 20–55% for Roux-en-Y gastric bypass),<sup>47</sup> we also check iron studies in people who had gastric sleeve procedures. In pregnancies after metabolic and bariatric surgery, we typically follow ACOG's recommendations for the frequency of screening, which is once a trimester,<sup>48</sup> and supplement with oral formulations initially when deficiencies are found and then intravenous or intramuscular formulations if there is an inadequate response. For people with a history of malabsorptive procedures, additional monitoring for fat-soluble vitamins (A, D, E, and K), zinc, and

**Table 2. Additional Screening and Supplementation Considerations**

Condition	Additional Screening Recommended	Additional Supplements Recommended
History of bariatric surgery, malabsorptive type	Every-trimester vitamin B <sub>12</sub> level, folic acid level, iron panel, vitamin D level Consider additional monitoring for fat-soluble vitamins (A, D, E, and K), zinc, and copper Nutrition consult	Supplementation based on results of screening
History of bariatric surgery, restrictive type	Every-trimester vitamin B <sub>12</sub> level, additional every-trimester iron panel for history of gastric sleeve procedure Nutrition consult	Supplementation based on results of screening
Inflammatory bowel disease	First-trimester iron panel and vitamin B <sub>12</sub> level	Supplementation based on results of screening
Multiple gestation	No additional screening Nutrition consult	1,000 micrograms of folic acid daily, 1,000 international units of vitamin D daily, 2,000–2,500 mg calcium daily
Prior neural tube defect	No additional screening	4,000 micrograms of folic acid daily until at least the end of the first trimester
Pregestational diabetes	No additional screening	No additional supplementation
Seizure disorder treated with certain antiepileptic medications	No additional screening	No additional supplementation
Anemia, iron deficiency	First-trimester screening with complete blood count followed by iron panel if anemia is detected	Daily oral 65 mg elemental iron supplementation or more based on results of screening; consider intravenous iron if indicated
Anemia, vitamin B <sub>12</sub> or folate deficiency	First-trimester screening with complete blood count followed by iron panel and subsequently folate and vitamin B <sub>12</sub> level screening	Supplementation based on results of screening
Vegetarian or vegan diet	No additional screening based on identification of vegetarian or vegan diet alone but could consider screening for iron, vitamin B <sub>12</sub> , vitamin D, and calcium on a clinical basis for diets without dairy and a nutrition consult	Supplementation based on results of screening

copper may be indicated, depending on other clinical factors.<sup>47</sup> In addition to targeted supplementation, people may be prescribed specialty bariatric supplements after metabolic and bariatric surgery. We recommend that clinicians be attentive to the formulations of these supplements to ensure that they contain adequate folic acid for the prepregnancy and pregnancy states and avoid supplements that include the retinol form of vitamin A. In general, we do not recommend taking both a prenatal vitamin and a bariatric supplement. Instead, we recommend taking a prenatal vitamin along with additional supplementation as needed for detected deficiencies. We recommend a referral to a nutritionist to help guide this management.

### Inflammatory Bowel Disease

People with inflammatory bowel disease are at increased risk of iron and B<sub>12</sub> deficiency. These levels

should be checked in the first trimester, and supplements should be provided as indicated.<sup>49</sup> There is currently no strong recommendation for increased folic acid supplementation beyond 400 micrograms daily as recommended for the general pregnant population.<sup>49</sup> Some people may experience additional gastrointestinal distress with oral iron formulations in prenatal vitamins. We recommend a patient-centered discussion and consideration of intravenous iron formulations, if indicated.

### Multiple Gestation

Anemia attributable to folate deficiency is eight times more likely in twin pregnancies; thus, we recommend supplementation with a total of 1,000 micrograms folic acid daily compared with the 400 micrograms recommended for singleton pregnancies.<sup>2</sup> Additional supplementation with 1,000 international units of vitamin D (compared with 600 international units/d for

singletons) and 2,000–2,500 mg calcium per day (compared with 1,000–1,300 mg/day for singletons) is also recommended to support maternal and fetal bone health.<sup>2</sup> There are no established guidelines for supplements in higher-order multiples. We provide similar supplements to higher-order multiples and twin gestations. A referral to a nutritionist is recommended to help guide this management.

### **Prior Neural Tube Defect**

People with a personal or family history of neural tube defects or those with a prior pregnancy affected by a neural tube defect, including anencephaly, encephalocele, or spina bifida, should receive high-dose folic acid supplements.<sup>50</sup> Robust evidence supports folic acid supplementation in reducing the risk of neural tube defects. Administration of folic acid before pregnancy reduced both the first occurrence of fetal open neural tube defects and the subsequent occurrence of fetal open neural tube defects by an estimated 70%.<sup>50</sup> We recommend 4 mg folic acid daily in the 3 months before pregnancy and until at least the end of the first trimester.<sup>34,51</sup> For people who require additional folic acid supplements, we do not recommend more than one daily prenatal vitamin and instead prescribe separate folic acid supplements to avoid an excess of other nutrients found in prenatal vitamins. This action translates into people taking additional pills to meet the higher folic acid requirements because folic acid supplements usually come in 1 mg tablets.

### **Type 1 Diabetes Mellitus and Pregestational Diabetes**

Pregnancies complicated by preexisting type 1 diabetes or other forms of pregestational diabetes are associated with an increased risk of neural tube defects. Some international guidelines recommend enhanced folic acid supplementation<sup>52</sup> with daily doses of 1 mg, whereas the World Health Organization, Royal College of Obstetricians and Gynaecologists, and Royal Australian and New Zealand College of Obstetricians and Gynaecologists advocate for 5 mg/d.<sup>52,53</sup> However, ACOG continues to recommend standard folic acid supplements in people with pregestational diabetes.<sup>34</sup> In line with ACOG's recommendations, we recommend standard folic acid supplements in people with diabetes.

### **Seizure Disorder Treated With Valproate or Carbamazepine**

People with seizure disorders treated with teratogenic medications such as valproate or carbamazepine are at heightened risk for neural tube defects in their

fetuses. However, these medications have also been associated with folate-resistant neural tube defects. Although previous recommendations included a daily intake of 1 mg folic acid to mitigate teratogenic effects,<sup>54</sup> high-dose folic acid supplements for those taking antiepileptic medications are no longer recommended by ACOG.<sup>34</sup> The American Academy of Neurology similarly recommends standard dosing of 400 micrograms folic acid before pregnancy for those with epilepsy treated with antiepileptic drugs.<sup>55</sup>

### **Anemia**

ACOG recommends screening for anemia with a complete blood count in the first trimester and again at 24 0/7–28 6/7 weeks of gestation and proceeding with further evaluation if the hematocrit level is less than 33% in the first and third trimesters or less than 32% in the second trimester.<sup>56,57</sup> Furthermore, unless there are patient-specific contraindications, including history of hemochromatosis, thalassemia, or other conditions that result in hemolytic anemia, the ACOG and the Centers for Disease Control and Prevention recommend universal low-dose iron supplements to prevent maternal anemia at delivery.<sup>56,57</sup> If anemia is detected, the appropriate evaluation includes iron (ferritin, total iron binding capacity, iron), folate, and vitamin B<sub>12</sub> levels, depending on the mean corpuscular volume and other clinical or individual risk factors.<sup>57</sup> If there is no clinical suspicion for folate or vitamin B<sub>12</sub> deficiency, we favor checking an iron panel first and, if iron deficiency is not detected, proceeding with evaluating folate and vitamin B<sub>12</sub> levels.

Management of anemia during pregnancy depends on the cause. For iron-deficiency anemia, supplements with high-dose (at least 65 mg elemental iron) oral iron is the first-line treatment.<sup>56</sup> In nonpregnant women, oral iron supplements given on alternate days may have similar or even possibly improved efficacy compared with daily dosing, with the benefit of fewer gastrointestinal side effects compared with continuous use.<sup>58,59</sup> A small randomized controlled trial conducted in 88 pregnant people with iron-deficiency anemia found no difference in hemoglobin after 6 weeks of treatment between those given alternate-day iron supplements (2 tablets of 325 mg ferrous sulfate every other day) compared with once-daily dosing, and adverse effects were similar.<sup>60</sup> Another randomized controlled trial in pregnant people found no difference in the change in hemoglobin, hematocrit, ferritin, or hepcidin levels after 6 weeks of daily or alternate-day oral iron supplements.<sup>60</sup> Given that more frequent iron intake increases hepcidin, which then impairs iron absorption, this finding is of

interest. The association between iron intake and hepcidin potentially explains why alternate-day dosing is considered more efficacious in the nonpregnant population. In general, we recommend alternate daily dosing of iron supplements as an option for those with gastrointestinal side effects from oral iron supplements.<sup>56,60</sup> Common iron formulations include ferrous sulfate (65 mg elemental iron per tablet), ferrous fumarate (106 mg elemental iron per tablet), and ferrous gluconate (28–36 mg elemental iron per tablet).

Intravenous iron infusions should be considered if pregnant people cannot tolerate or do not have an adequate response to oral supplements.<sup>56</sup> In a randomized controlled trial in Denmark of 201 pregnant people who received a single dose of 1,000 mg intravenous iron isomaltoside compared with 100-mg elemental oral iron supplements daily, the hemoglobin increase was higher in the intravenous compared with the oral iron group at 6, 12, and 18 weeks after treatment.<sup>61</sup> A recent expert panel consensus recommended intravenous iron supplements as first-line treatment, especially in the second and third trimesters.<sup>62</sup> However, intravenous iron may be more expensive and less accessible compared with oral supplements. Therefore, we continue to recommend oral iron supplements as first-line treatment with a caveat that it is reasonable, depending on the severity of iron deficiency and gestational age, to give intravenous iron as first-line treatment if available. Finally, other clinical considerations, including a person's inability to tolerate oral medications or history of a malabsorptive condition, may require intravenous iron as the first-line treatment.

In cases of vitamin B<sub>12</sub> or folate deficiency, targeted supplementation of either vitamin B<sub>12</sub> or folate (1 mg folic acid daily) is necessary. Treatment of vitamin B<sub>12</sub> can start with high oral doses (1,000–2,000 micrograms daily) but may require intramuscular forms, depending on the severity of the deficiency and other clinical factors. One option for treatment is 1,000 micrograms intramuscular vitamin B<sub>12</sub> three times a week for 2 weeks, followed by 1,000 micrograms once a month.<sup>63</sup> In our practice, we typically repeat testing for the deficient factors (iron studies, folic acid, vitamin B<sub>12</sub>) approximately 1 month after supplementation began to ensure normalization of the values. In people with sickle cell disease (hemoglobin SS disease), in addition to other hematologic conditions complicated by hemolytic anemia, routine iron supplementation is avoided unless iron deficiency is confirmed to avoid risks of iron overload secondary to chronic hemolysis and blood transfusions.<sup>64</sup> In addition,

as a result of increased red blood cell turnover in people with sickle cell disease, it is recommended that these people take 4 mg folic acid daily for the duration of the pregnancy.<sup>64</sup>

## Dietary Considerations

Balanced vegetarian diets that incorporate dairy and eggs typically meet macronutrient needs; however, protein intake may occasionally be insufficient. Strict vegan diets present a higher risk for deficiencies, particularly in iron, vitamin B<sub>12</sub>, vitamin D, calcium, and PUFAs. Furthermore, diets high in beans and whole grains containing phytates may impair zinc absorption, necessitating additional zinc supplements. Screening for such vitamin deficiencies in people with restrictive diets should be considered on a clinical basis. We recommend a consultation with a nutritionist for people who follow a vegan diet.

## Supplements for Prevention of Preeclampsia

Studies addressing the use of supplements to prevent or reduce the risk of preeclampsia are not novel, but more recent investigations include calcium, vitamin D, and L-arginine supplements.<sup>65–67</sup> A Cochrane review of 27 studies found that *high-dose calcium supplements*, defined as 1 g or more daily, significantly reduced the risk of preeclampsia.<sup>65</sup> This effect was particularly pronounced in women with *low dietary calcium intake*, defined as less than 900 mg daily. Moreover, the World Health Organization recommends a 1.5- to 2-g calcium supplement daily<sup>68</sup> in populations in whom calcium intake is low.

Observational studies have associated vitamin D deficiency with preeclampsia, and randomized controlled trials have shown a reduction in preeclampsia with vitamin D supplements,<sup>66</sup> although the effects on short- and long-term neonatal outcomes remain uncertain.<sup>69</sup> The mechanism for this finding is thought to be related to the reduction of oxidative stress, the regulation of endothelial function, and the modulation of angiogenesis.<sup>70</sup> Vitamin C supplements, in comparison, were not shown to reduce preeclampsia risk in a 2015 Cochrane review of 29 trials.<sup>16</sup>

L-Arginine, a nitric oxide precursor, has also been studied for preeclampsia prevention. It is posited to oppose vasoconstriction as part of the dysregulated angiogenesis that occurs in the pathogenesis of preeclampsia.<sup>67</sup> A recent meta-analysis of 20 randomized controlled trials and three nonrandomized trials found that L-arginine was associated with a reduced risk of preeclampsia (relative risk 0.52, 95% CI, 0.35–0.78 in four prevention trials) and severe preeclampsia (relative risk 0.23, 95% CI, 0.09–0.55 in three prevention

trials), although further work is needed in this area, given that the risk of bias was high in several of the trials and given the lack of large randomized controlled trials.<sup>67</sup> Optimal dosing and timing of L-arginine supplements should be well defined before any recommendation is made for clinical practice.

At this time, the only medication recommended by the ACOG for prevention of preeclampsia in select populations is low-dose aspirin (81 mg); we concur with this recommendation but note that promising research is ongoing.

## CONCLUSION

The need for additional supplements in the perinatal period is driven by nutritional needs for fetal growth in addition to the metabolic demands of pregnancy. Prepregnancy counseling is an important part of optimizing nutrition for future pregnancy and should include discussion of a prenatal vitamin or the equivalent dietary micronutrients. Clinicians should be aware that prenatal vitamins are minimally regulated and require attention to their nutritional content when prescribing or recommending a supplement. Future policy and advocacy work is warranted to regulate and standardize prenatal vitamins to better meet nutritional recommendations in pregnancy.

Access to supplements and sufficient nutrition is shaped by socioeconomic factors and requires careful consideration and counseling in the perinatal period. Further investigation is needed with pregnancy-specific validated screening tools of social drivers of health to better target supplements for those at risk for nutritional deficiencies.

Although prenatal vitamins remain the mainstay of supplements in conjunction with a balanced diet, preexisting comorbidities and nutrient deficiencies may necessitate extra supplementation. Research to describe the additional benefits of supplements in the prevention of pregnancy-related comorbidities such as hypertensive disorders of pregnancy represents a growing area of work.

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