

# Physiological Need for Calcium, Iron, and Folic Acid for Women of Various Subpopulations During Pregnancy and Beyond

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## Abstract

Women tend to supplement their diets with multivitamin/mineral (MVM) supplements more often than men, and reports indicate that more than 90% of pregnant women in the United States supplement their diets with prenatal MVMs. Given the widespread use of MVMs among women and given the increasing efforts to unveil the importance of phenotype-specific health determinants, it seems imperative to review what is known about variations in nutrient physiology among women from different ethnic and racial groups and at different reproductive stages of life. In this study, we embark on an assessment of the scientific evidence and knowledge gaps that impact the precise determination of nutrient levels (specifically calcium, iron, and folic acid) that confer benefits to various subpopulations of women in the United States.

**Keywords:** calcium, folic acid, iron, pregnancy

**D**URING PREGNANCY, WOMEN are advised to consume higher levels of calcium, iron, and folic acid. As research continues to unveil the importance of phenotype-specific health determinants, it is critical to review what is known about nutrient physiology and how it may vary among women from different ethnic and racial groups and at different reproductive stages of life. This article presents the current understanding of calcium, iron, and folic acid physiology; related health consequences for women; and research gaps that impact the precise determination of nutrient levels and intake practices that confer health benefits to women.

## Calcium

Calcium, an essential element available only through dietary sources, is responsible for maintenance of the electric gradient across membranes, bone formation, and enzyme and

hormone functioning. Stored largely in bone (99%), calcium is essential for muscle contraction, bone and tooth development, blood clotting, nerve impulse transmission, heart rhythm regulation, and fluid balance within cells.<sup>1,2</sup>

Calcium balance is a function of dietary intake, intestinal absorption, renal excretion, and bone remodeling. The three latter mechanisms are regulated by the parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], and ionized calcium, along with receptors in the intestine, kidney, and bone that correspond to these hormones.<sup>3</sup> Hypercalcemia, frequently caused by primary hyperparathyroidism and malignancy, is associated with depression, lethargy, coma, muscle weakness, and constipation.<sup>1</sup> Hypocalcemia—normally caused by medication, medical treatment, or disease processes—can result in convulsions, paresthesia, cramps, and tetany.<sup>1</sup> Dietary deficiency can cause muscle cramping, dry skin, and brittle

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nails. It can also lead to osteoporosis and its associated effects, including bone deterioration and increased risk of fractures.<sup>2</sup>

Calcium requirements vary in women, depending on their reproductive stage.<sup>4,5</sup> Calcium bone stores fluctuate throughout a woman's life, with absorption from the diet gradually declining in adulthood.<sup>5</sup>

Bone growth occurs slowly during early childhood, increases quickly during puberty, and peaks between 25 and 30 years of age. Inadequate calcium intake can cause several problems in growing children and adolescents, including stunted growth and reduced peak bone density.<sup>6,7</sup>

During pregnancy, the efficiency of intestinal calcium absorption doubles, whereas during lactation, the maternal skeleton is resorbed to provide calcium for milk. Calcium intake remains especially critical during pregnancy and lactation because of the potential adverse effect on maternal and fetal bone health if maternal calcium stores are depleted. Since both the fetus and breastfed newborn are dependent on maternal sources for their total calcium, adequate maternal calcium intake can also affect fetal bone health positively.<sup>8</sup>

Inadequate calcium during pregnancy also impacts the development of pregnancy-related hypertensive disorders. Low calcium intake may stimulate PTH secretion, increasing intracellular calcium and smooth muscle contractions. Additionally, it can cause the release of renin from the kidney, leading to vasoconstriction and retention of sodium and fluid. These changes can lead to the development of pregnancy-induced hypertension (PIH) and preeclampsia.<sup>9</sup>

At menopause, a decline in intestinal calcium absorption and/or an increase in urinary calcium excretion may occur, leading to deterioration in calcium balance.<sup>10,11</sup> Recent data (2015) from clinical trials suggest that the effect of supplemental calcium is minimal or nonexistent for fracture prevention.<sup>12</sup>

Although numerous health consequences of calcium insufficiency and surplus are found in all populations,<sup>13–15</sup> data suggest that calcium metabolism and utilization differ by ethnicity.<sup>16,17</sup> Black adolescents absorb and retain calcium more efficiently than Whites, and bone turnover is greater in Blacks, favoring net bone accretion. These differences may account for bone mass differences observed in adulthood.<sup>18</sup> The incidence of osteoporosis and osteopenia is greater among non-Hispanic White and Asian adult women than among non-Hispanic Black and Hispanic women of all races. Peak bone mass, a predictor of fracture risk, is highest in Black women, who have the lowest incidence of fracture, lower in Hispanic and non-Hispanic White women, and lowest in Asian American women. However, some Asian subgroups with very low peak bone mass also have lower fracture rates. Ethnic variations in bone metabolism may be related to inherited genetic polymorphisms. Among ethnic groups, there are variations in acid metabolism, resulting in ethnic variations in sodium and calcium excretion rates; differences in bone turnover; and differences in intestinal calcium absorption. Such variations in metabolism may explain higher bone mineral density in African Americans.<sup>19</sup>

Given that adequate calcium intake during pregnancy and lactation is critical for the health of both mother and fetus and that most women do not consume the recommended quantity of calcium at any time in their lives, calcium supplementation is considered.<sup>9</sup> Two meta-analyses indicate the potential positive impact of calcium supplementation on PIH and preeclampsia. The first study demonstrated that the additional intake of calcium

during pregnancy is an effective measure to reduce the incidence of preeclampsia, especially in populations at high risk due to ethnicity, gender, age, high body-mass index, and low baseline calcium intake.<sup>20</sup> The second study suggests that for women with low calcium intake, calcium supplementation greater than 1 g per day may reduce the risk of preeclampsia, preterm birth, maternal deaths, and serious morbidities, but not stillbirth or admission to neonatal high care.<sup>21</sup> The limited data on low-dose calcium supplementation suggest a reduction in preeclampsia, hypertension, and admission to neonatal high care.

Because calcium intake tends to decrease with age, calcium supplementation is especially important in postmenopausal women. In addition, because of a decrease in estrogen production after menopause, women's bodies are less able to retain calcium from dietary sources. Consequently, calcium supplementation has been used for decades to prevent calcium depletion, maintain bone mass, and prevent and treat osteoporosis.<sup>22,23</sup>

## Iron

Iron is an essential nutrient that assists with the transfer of oxygen from the lungs to bodily tissues. A diet deficient in iron can negatively impact muscle metabolism, cognitive development, and growth. Excess iron intake results in oxidative stress, which is associated with hemochromatosis, some cancers, premature aging, neurodegenerative diseases, and atherosclerosis.<sup>24</sup>

Sex differences with respect to physiologic requirements for iron intake are well established. Adult females require more iron than adult males because of the loss of iron in their blood during menses. On the other hand, preadolescent males show a higher prevalence of iron deficiency anemia than preadolescent females. Iron levels tend to increase in postmenopausal women and decrease in males of similar age and status.<sup>25</sup> The Food and Nutrition Board at the National Academies of Sciences, Engineering, and Medicine therefore recommends higher dietary allowances of iron for females aged 14–50 years than for their male counterparts. In addition, because the physiologic requirements of iron in females are further complicated by pregnancy and lactation, current recommendations support higher dietary allowances of iron in pregnant females and lower dietary allowances of iron in lactating females than in nonpregnant and nonlactating females.<sup>26</sup>

In fact, maternal physiologic iron requirements fluctuate throughout pregnancy. During the first trimester, iron requirements decrease because of the cessation of menses, and iron stores may increase. During the second trimester, physiologic iron requirements increase due to expansion of maternal blood volume and red cell mass. Linear increases in iron requirements continue through the third trimester as iron accumulates in the placenta to support the development of infant red blood cells.

In healthy pregnant women with adequate prepregnancy iron stores, the increased iron requirements are balanced by more efficient iron absorption from the diet, improved oxygen delivery to the tissues, and increased heart output.<sup>27</sup> Assuming that 300 mg of stored iron reserves are adequate in prepregnant females, then ~50% of women in the United States achieve this status.<sup>27</sup> On the other hand, as many as 35% of women in the United States have depleted or nearly depleted iron reserves and are considered iron deficient.<sup>27</sup> To offset a potential imbalance in iron reserves during pregnancy and prevent maternal iron deficiency anemia, routine iron supplementation is widely practiced.

The U.S. Preventive Services Task Force (USPSTF) has published a statement indicating that evidence is insufficient to warrant routine iron supplementation during pregnancy.<sup>28</sup> Current published evidence on the benefits and risks of routine iron supplementation during pregnancy tends to focus more on infant outcomes and less on maternal health. With respect to maternal health, physiologic requirements for iron intake—and thus the benefits and risks of routine iron supplementation—are complicated by confounding factors, including ethnicity, diet, lifestyle, genetics, preexisting chronic diseases and conditions, and methods for assessing precise measures of iron status.

Iron status is commonly assessed as a measure of hemoglobin concentrations. However, interpretations of the outcomes of these measures are problematic. For example, iron deficiency as a measure of hemoglobin concentration is not always associated with anemic outcomes in all populations. On the other hand, measures of serum ferritin, a biomarker for iron stores, are more often preferred as a metric for low iron status.<sup>29</sup> Interpretations of high ferritin concentrations also have proven to be problematic. Because ferritin acts as an acute phase reactant to infection and inflammation, it is difficult to discern whether high levels of serum ferritin are indicative of an iron overload status or inflammation.<sup>30</sup> Furthermore, data from the Hemochromatosis and Iron Overload Screening Study of 20,080 nonpregnant and 1962 pregnant women suggest innate biological differences in serum ferritin levels (as well as transferrin saturation) across racial and ethnic groups and also suggest that these measures must be interpreted differently in persons of Asian or Pacific Island heritage than in Whites.<sup>31</sup> Similarly, differences between the interpretation of maternal hematocrit levels in Black pregnant women and in White pregnant women have been reported.<sup>32,33</sup>

Improved assessments of maternal iron status are crucial for determining for which individuals and to what extent iron supplementation might improve maternal health outcomes. High ferritin levels (even after accounting for inflammatory status) have been associated with insulin resistance, type 2 diabetes, and hypertension. A recent meta-analysis suggests that consumption of dietary heme iron may exacerbate the onset of gestational diabetes mellitus (GDM).<sup>34,35</sup> Less is understood about the role of iron supplements and the onset of GDM. While nonheme forms of iron found in iron supplements are much less readily absorbed than dietary heme iron, some evidence suggests that in iron-replete women, consumption of iron supplements may result in increased amounts of unabsorbed iron in the intestine, damage of pancreatic  $\beta$  cells, increased insulin resistance, and subsequent development of diabetes.<sup>29,34</sup>

These outcomes are especially relevant given the alarming rates of maternal morbidity in the United States. Precise recommendations of iron intake within the context of ethnicity, life stage, and preexisting conditions may offer a potential opportunity to mitigate risk factors associated with maternal morbidity.

### Folic Acid

Folate, or vitamin B9, is a water-soluble vitamin that the body utilizes to synthesize nucleic acids (DNA and RNA) and to metabolize amino acids for cell growth. Although it is found in many foods (dark leafy greens, peas and beans, and fruits), many countries fortify grain and cereal products with folic acid (synthetic folate).

One of the benefits of folate when taken during pregnancy is the prevention of fetal neural tube defects (NTDs). Folate and folic acid also have shown benefits or potential benefits in the treatment of cardiovascular disease<sup>36–38</sup> and diabetes,<sup>39</sup> cancer and antiviral therapies,<sup>40,41</sup> longer term neurological development in infants and neurological status in adults,<sup>42</sup> treatment of such chronic diseases as arthritis<sup>43</sup> and sickle cell disease,<sup>44</sup> reduction of the effects of radiation exposure,<sup>45</sup> and improvement in neurocognitive function<sup>42</sup> and as additives in various treatments and medications.

Although the benefits of folic acid supplementation in preventing NTDs are clear, some concerns are associated with increased folate and folic acid intake. Folic acid supplementation may mask an existing vitamin B12 deficiency.<sup>46</sup> Additionally, some studies have linked excess folic acid intake with increased risk of the development and recurrence of certain types of cancers.<sup>47</sup>

No gender-specific differences in folate or folic acid metabolism or biological requirements for men and women have been reported, except to accommodate reproductive differences. The National Institutes of Health's Office of Dietary Supplements recommends identical folic acid intake requirements for men and women throughout the life span, increasing from 65  $\mu\text{g}$  of dietary folate equivalents (DFE) at time of birth and up to 6 months to 400  $\mu\text{g}$  DFE in adulthood, with increases for pregnancy and lactation.<sup>48</sup>

Although studies show that most Americans have an adequate dietary intake of folate, pregnant women, teens, and other groups may have insufficient levels of folate.<sup>49</sup> The USPSTF recommends that women who are planning to or could become pregnant take a folic acid supplement of 0.4 to 0.8 mg daily to prevent NTDs. For maximum effectiveness, the supplementation must begin in the month before pregnancy and continue to the second or third month.<sup>50</sup>

Because of the high rate of unplanned pregnancy and the potential serious effects of folate deficiency, the Food and Drug Administration has mandated the fortification of such U.S. grain products as pasta, rice, and cereals since January 1998 and of corn masa flour since April 2016.<sup>51</sup>

Estimating racial and ethnic differences in both folate and folic acid synthesis and the effects of fortification and supplementation on outcomes has been difficult. Supplementation with folic acid had less of an effect on maternal and cord blood sample folates for African Americans.<sup>52</sup> A study of women living in Georgia found that ~25% of women were taking a folic acid supplement preconception, with non-Hispanic women twice as likely as Hispanic women to take folic acid supplements.<sup>53</sup> In terms of differences in metabolism, among women taking folic acid supplements, the largest increase in folate levels was noted in White women, followed by Hispanic women, with Black women experiencing the lowest serum folate levels.<sup>54</sup>

Underlying conditions also affect folate levels and risk for NTDs. Hispanic women are more likely than other groups to have the MTHFR C677T gene variant, which can result in impaired folic acid processing.<sup>55</sup> People with alcohol use disorder, inflammatory bowel disease, celiac disease, gastric surgeries, and gastritis may be at risk for impaired folic acid absorption.<sup>56</sup> Ethnic and racial variations in the prevalence of these conditions affect the physiology of folic acid.

When identifying the success and cost-benefit analysis of folic acid food enrichment, it is important to take cultural foods into account. Many wheat and other cereal-based

products have been approved for enrichment, but many other grain-based foods have not; corn flour was not required to be enriched until 2016, which is significant because corn flour is commonly used in traditional Hispanic foods. The rates of folic acid consumption for Hispanics have been consistently lower than for Caucasians.<sup>57</sup>

### Conclusions

Despite the wealth of research on calcium, iron, and folate and their effects on women's health outcomes, most studies conducted in the United States either included only White women or, when mixed ethnic/racial groups were included, the studies lacked adequate representation of specific groups that would allow appropriate subgroup analyses. Studies of specific ethnic and racial groups tend to be small and are inconsistent across all populations. Large longitudinal studies with adequate representation across ethnic and racial groups, which allows cross-group and intragroup comparisons, are needed. Intragroup analyses should separate regional differences or countries of origin since different cultural habits impact dietary intake and thus risk for certain diseases.

Additionally, intake data, generally obtained through dietary and supplement adherence recall methods, may not adequately capture the variation in the amount of each nutrient and their bioavailability in various supplements, the differences between the bioavailability of nutrients in food and supplements, and variations in prescribed intake protocols (for high-risk vs. low-risk groups). Research using standardized supplement doses or more carefully controlled dietary monitoring would improve the reliability of the data.

Finally, methodologies used to study health outcomes need to be refined. For example, bone health studies vary in bone test sites used, reporting methods, and sample sizes. Studies are needed to better determine the etiology of diseases related to calcium, iron, and folic acid within different population subgroups and should include larger high-quality trials.

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