Dietary Intake Influences Vitamin Needs during Pregnancy

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Contributor: Riccardo Ientile, Maria Paola Bertuccio, Monica Currò, DANIELA CACCAMO

Numerous approaches demonstrate how nutritional intake can be sufficient to ensure the necessary supply of vitamins. However, it is evident that not all vitamins are contained in all foods, so it is necessary either to combine different food groups or to use a vitamin supplement to be well-fed. During pregnancy, deficiencies are often exacerbated due to increased energy and nutritional demands, causing adverse outcomes in mother and child. Micronutrient supplementation could lead to optimal pregnancy outcomes being essential for proper metabolic activities that are involved in tissue growth and functioning in the developing fetus. In order to establish adequate vitamin supplementation, various conditions should be considered, such as metabolism, nutrition and genetic elements.

Keywords: vitamin B9 ; pregnancy ; water-soluble vitamins

1. Relevant Findings on Water-Soluble Vitamins

The most relevant literature data on critical issues related to the supplementation of water-soluble vitamins in pregnant women are discussed in the following paragraphs.

Normal reference levels and recommended intake, when available, of each vitamin in different physiological conditions, have been derived from literature data, DRI reports, and Institutes of Medicine National Academy (see www.nap.edu accessed on 3 March 2022), and are shown in **Table 1**.

Table 1. Plasma levels and reference values for the intake of water-soluble vitamins B9, B12, B1, and C.

Water-Soluble Vitamins	Plasma Levels	Nutrient Intake under Physiological Conditions	Recommended Intake in Early Pregnancy	Recommended Intake in Late Pregnancy	References
Vitamin B9	2.2–17 ng/ml	400 µg/day	600 µg/day	500 µg/day	[1]
Vitamin B12	2–9 µg/ml	2.4 µg/day	2.6 µg/day	2.8 µg/day	[2]
Vitamin B1	5–12 µg/dL	1.2 mg/day	1.4 mg/day	-	[3]
Vitamin C	6–14 mg/L	75 mg/day	85 mg/day	120 mg/day	[4]

2. Folic Acid

Folic acid (vitamin B9) is an essential nutrient required for the synthesis of nucleic acids and heme group, and for protein metabolism. Thus, it is critically needed during periods of rapid growth, such as during pregnancy and fetal development.

Foods that are good sources of folate are dark green leafy vegetables (spinach, broccoli, romaine lettuce, turnip greens, asparagus, Brussels sprouts), fresh fruits, beans, peanuts, sunflower seeds, eggs, liver, whole grains, and seafood, among foods (see www.nap.edu accessed on 3 March 2022).

Vitamin B9, together with a multivitamin supplement, during pregnancy or in women of reproductive age, may be useful to reduce occurrence of birth defects. In Western society, vitamin B9 intake may be sufficient. Instead, in some population folate-multivitamin supplementation can be necessary and should be assumed once daily. The recommended intake in early and late pregnancy is increased by 50% and 25%, respectively, compared with normal requirement (**Table 1**).

Vitamin B9 supplementation during pregnancy is known to protect the fetus from neural tube defects. Furthermore, tetrahydrofolate plays an important role in the metabolism of the one-carbon units involved in the epigenetic regulation of transcription which underlies development. Therefore, unexpected persistent effects in the offspring may be caused by maternal folic acid supplementation, as suggested in a review [5]. A more recent review claims that, although fortification of grains with vitamin B9 may be useful for public-health outcome, further investigations are needed to ascertain if excessive folic acid intakes increasing methyl group availability may have potential hazardous effects on newborns [6]. In addition, a case report described small intestine perforation after ingestion of a high amount of vitamin B9 supplements [7].

Vitamin B9 works closely with vitamin B12 in the re-methylation cycle that produces methionine from homocysteine (Hcy) [6]. Vitamin deficiency leads to elevated homocysteine levels, namely hyperhomocysteinemia, that has been identified as an independent risk factor for the development of atherosclerosis and other inflammation- and oxidative stress-related conditions.

Recent data suggested that suitable approaches for the prevention of exceeding folate intake may critically depend on the underlying mechanisms of biochemical defects. Folate status and hyperhomocysteinemia usually are determined by poor dietary intake, unhealthy lifestyle (i.e., alcohol excess), and the presence of common genetic variants, such as methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms [8].

Several studies focused on the association between SNPs of MTHFR gene and increased risk of adverse birth outcomes [9][10][11][12][13].

However, intervention with folic acid alone may not only be inefficient, but even cause harm to women living in regions where vitamin B12 deficiency is endemic [14].

A common polymorphism in the MTHFR gene is represented by cytosine to thymine substitution at position 677 in exon 4 (MTHFR C677T). This substitution leads to the insertion of valine for alanine in the corresponding protein resulting in a reduction in enzyme activity [15] and accumulation of plasma Hcy [9].

MTHFR polymorphisms are known to reduce the bioavailability of folate and have been linked to pregnancy complications such as preeclampsia (PE) and intrauterine growth restriction (IUGR) [16][17][18].

A meta-analysis performed by Chen et al. in 2016, by considering studies published before August 2014, found that there was no association of the MTHFR C677T polymorphism with pre-term birth (PTB) or placental abruption [9].

A recent meta-analysis evaluated both the maternal and neonatal MTHFR C677T polymorphism confirming that there is a conclusive association between maternal MTHFR C677T polymorphism and preterm birth (PTB) as well as low birth weight (LBW) risk and no significant association between neonatal MTHFR C677T polymorphism with PTB or LBW [19].

Based on development status, this meta-analysis showed that there is a statistically significant association between the maternal MTHFR C677T polymorphism and PTB as well as LBW risk in developing countries in comparison with results obtained in studies from developed countries. These findings are not surprising as pregnant women in developing countries might not intake folate adequately as opposed to their counterparts in developed countries [20].

Moreover, it is well-known that women with the MTHFR 677TT genotype are predisposed to increased plasma homocysteine levels when folate intake is insufficient; thus pregnant woman with TT genotype in developing countries are more likely to give birth to babies with PTB or LBW [21].

It has been found that MTHFR 1298CC was associated with increased risk for PE, whereas there was an association between the maternal transcobalamin 2 (TCN2) 776GG genotype and a decreased risk for spontaneous preterm births [22].

TCN2 polymorphism (C > G substitution) alters the structure of the TCN2 protein modifying its affinity for vitamin B12, resulting in an easier release from the bound TCN2 transporter with a consequent reduced vitamin B12 transport into cells and thus higher Hcy levels compared with the CC genotype. The authors showed that folic acid supplementation leads to higher serum folate and vitamin B12 concentrations, a reduced uterine artery resistance index, and increased birth weight [23].

Higher circulating Hcy levels were also found in pregnant woman with the MTHFD1 G1958A mutation, which can result in a reduction in the stability of its synthetase domain, modifying its metabolic activity to limit the availability of methyl THF

[24]. The AA genotype is also associated with neural tube defects and cardiac malformations in humans as MTHFD1 enzyme function is involved in purine synthesis and pregnancy outcome [25].

Different approaches for the prevention or reduction of congenital anomalies should take into account the age of subjects, ethnicity, compliance, and genetic risk conditions [26][27].

3. Vitamin B12 and Vitamin B1

Vitamin B12 is an essential micronutrient, naturally present in eggs, fish, meat, poultry, and dairy products, and only in small amounts in vegetables. Other than in Hcy metabolism, vitamin B12 is involved in the one-carbon units metabolism related to synthesis and stabilization of nucleic acids as well as in DNA methylation, required for the epigenetic regulation of gene expression. Moreover, vitamin B12 is needed for erythropoiesis as well as for development and myelination of nerve cells (see www.nap.edu accessed on 3 March 2022).

The recommended intake of vitamin B12 during pregnancy ranges from 2.6 to 2.8 µg/day (**Table 1**). Vitamin B12 deficiency may be a cause of infertility or recurrent spontaneous abortion and an inadequate vitamin B12 status at the beginning of a pregnancy may increase the risk of birth defects, such as neural tube defects [28].

No literature data are available regarding the influence of genetics on vitamin B12 status.

Vitamin B1, also known as thiamine, is a micronutrient with multiple functions in carbohydrate metabolism. Its deficiency leads to an impaired oxidative and energy metabolism, causing serious and potentially irreversible neurological damage or death [3].

The RDA of vitamin B1 can be met by the consumption of yeast, meat (beef, pork), liver, whole grains, germ of cereals, eggs, as well as fruits (oranges) and vegetables (pulses, kale, asparagus, cauliflower, potatoes).

It is well known that pregnancy and lactation require an increased thiamine need. The analysis of vitamin B1 concentrations showed that approximately 50% of women develop a biochemical thiamine deficiency during the trimesters of pregnancy [29]. The deficiency occurs particularly when dietary intake is inadequate or excessive alcohol is consumed, as reported in a recent review [30].

During pregnancy, thiamine requirements increase, probably as result of the vitamin sequestration by the fetus and placenta (**Table 1**).

In fact, thiamine and other water-soluble vitamins (B9, B12, and C) are 2–5 times more concentrated in the umbilical cord blood than in maternal blood [31]. Moreover, Ortega and colleagues confirmed that maternal thiamine intake influences mature breast milk thiamine concentration and the activation coefficient of erythrocyte transketolase (a-ETK) [32].

Regarding vitamin B1 toxicity, there is no determined tolerable upper intake level for thiamine. Thiamine transporters 1 (THTR1) encoded by the gene solute carrier family 19 member 2 (SLC19A2) and thiamine transporters 2 (THTR2) encoded by solute carrier family 19 member 3 (SLC19A3), perform the function of carrying thiamine to the cells. The enzyme thiamine pyrophosphokinase (TPK1) activates thiamine within the cell, forming thiamine diphosphate (TDP), a cofactor for several enzymes involved in the regulation of glucose metabolism. It is known that mutations in SLC19A2 and SLC19A3 are rare and they cause monogenic diseases, whereas variants in TPK1 are common and are associated with birth weight [33][34][35]. Bartáková et al. found that transketolase (TKT) activity, which requires vitamin B1 as a cofactor, in the postpartum depend on the genotypes of SLC19A2 SNP rs6656822 and SLC19A3 SNP rs7567984; the enzymatic activity is higher in homozygotes TT for the first one and in heterozygotes CT for the second one. The authors suggested that inter-individual variability in thiamine metabolism may be involved in the postpartum persistence of glucose and in the susceptibility to GDM [33].

4. Vitamin C

Vitamin C is a powerful antioxidant needed for regeneration of other antioxidants, such as vitamin E. Its antioxidant action has been reported to be protective against the development of oxidative stress-related disorders, such as cancer and cardiovascular diseases. Vitamin C also plays a key role in many biosynthetic pathways, i.e., synthesis of collagen and neurotransmitters, in immune function and in iron absorption by intestine. Vitamin C deficiency is associated with the development of scurvy, capillary fragility, and abnormal wound healing [35].

The RDA of vitamin C can be met by the consumption of fresh fruits (oranges, kiwi, lemon, strawberries, grapefruit) and vegetables (tomatoes, bell peppers, cabbage, broccoli, cauliflower, white potatoes), among foods (see www.nap.edu accessed on 3 March 2022).

On the basis of recent investigation, a role for vitamin C supplement in order to avoid preeclampsia, intrauterine growth restriction and maternal anemia has been proposed. Data analysis in a prospective cohort study involving 24,300 women clearly demonstrated that a vitamin C supplement is effective for the prevention of fetal or neonatal death, poor fetal growth, and preterm birth or pre-eclampsia [36].

For most people, the recommended doses of vitamin C are likely safe (**Table 1**); however, vitamin C at daily doses higher than 2000 mg might cause some adverse effects, such as vomiting, heartburn, and stomach cramps [37].

Taking into account the widespread use of vitamin supplements during pregnancy, the values of recommended intake should be indicated in a range of tolerable doses.

In an observational study conducted in North Carolina in 2064 women, low vitamin C intake, either before conception or during the second trimester, was associated with an elevated risk of preterm, premature rupture of the membranes. Women with low vitamin C intake during both time periods showed the greatest risk [38].

These observations suggest that genetic variants in vitamin C transport could contribute to the risk for preterm birth-related outcomes.

An electronic letter reported that vitamin C is transported by one of two sodium-dependent vitamin C transporters (SVCT1, encoded by SLC23A1 and mapped to 5q31.2; and SVCT2, encoded by SLC23A2 and mapped to 20p13) [39].

Erichsen and colleagues showed that three SLC23A2 individual SNPs were associated with preterm birth in White individuals, but after hierarchical regression analysis, only SLC23A2-08 (an intron 2 variant, rs6139591), was strongly associated. The authors found that individuals heterozygous for the T allele of SLC23A2-08 showed some elevation in risk, whereas individuals homozygous for the T allele had a nearly threefold elevated risk of preterm delivery [40].

Duarte-Salles et al. found a correlation between genotoxic airborne polycyclic aromatic hydrocarbons (PAH) benzo(a)pyrene [B(a)P] intakes and significant reduction both in birth weight and length, and an increase in risk of size for gestational age (SGA) among women with low dietary vitamin C intakes during the first trimester of pregnancy.

Among these women, associations were strongest in those carrying the glutathione S-transferase P1 (GSTP1) Ile105Val polymorphism, that is associated with lower contaminant detoxification activity. On the contrary, no association was found between dietary B(a)P and SGA among women with high vitamin C intake (OR: 0.81; 95% CI: 0.23–2.75). The authors did not observe significant interactions with vitamin E, alpha-carotene or beta-carotene intakes in associations between dietary B(a)P and fetal growth indicators [41].

5. Other Water-Soluble Vitamins

Few data are available regarding the role of other water-soluble vitamins during pregnancy. The requirement for some vitamins, such as nicotinamide (B3, niacin), riboflavin (B2), and biotin (vitamin B7) is, in most cases, ensured by the diet in developed countries. Adequate amounts of riboflavin and niacin are provided by enriched cereals and grain-containing products, whereas biotin can be mainly found in foods like eggs, milk, and bananas [42]. These vitamins act as co-factors of enzymes involved in the metabolism of lipids, carbohydrates, and other substrates, in energy production, and DNA repair, and can be also synthesized by intestinal bacteria [43].

Vitamin B6, in its main form pyridoxal phosphate, acts as a co-factor for numerous enzymes, involved in the catabolism of proteins, carbohydrates, and lipids, in homocysteine trans-sulfuration to cysteine, and in immune function and brain health. Six pyridine derivatives related to phosphorylation are indicated as vitamin B6.

The RDA of vitamin B6 can be met by the consumption of fish (salmon, tuna), meat (beef liver, poultry), legumes (chickpeas), some vegetables (dark leafy greens), and fruits (bananas, oranges, cantaloupe, papayas), among others (see www.nap.edu accessed on 3 March 2022).

Vitamin B6 supplementation influenced nausea and vomiting, and produced beneficial effects in dental health. In a meta-analysis based on three small studies, it has been reported that vitamin B6 supplementation had a significant positive effect on birth weight [44].

Vitamin B6 decreases physiologically during pregnancy probably due to the increase in blood volume. Perhaps this is why its deficient status has not been indicated in pregnant women with reduced parameter conditions [45].

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