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Original Communication

Vitamins for the First 1000 Days: Preparing for Life

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Abstract: Vitamins are essential nutrients for many body functions and particularly important during growth. Adequate supply in pregnancy and in early infancy is therefore crucial, but there is still a lack of knowledge about the needed amounts of vitamins of children older than six months and also during pregnancy. Recommendations for intake levels are generally derived by extrapolation from data for infants based in turn on the contents in breast milk and those for adults. A vitamin of particular importance in pregnancy is folic acid due to its role in the development of the brain and nerve system and the prevention of fetal neural tube defects (NTD). Mandatory fortification of flour and certain other grain products in many countries has been associated with a reduction in NTD incidence. However, other deficiencies or suboptimal status of B vitamins, especially B_6 and B_{12} have been repeatedly reported in pregnant women also in high-income countries. Vitamin A is one of the three most critical micronutrients globally and pregnant women and young children are especially vulnerable to deficiencies. Night blindness, anemia, and immunodeficiency are major consequences of inadequate supply in these populations. Much attention has recently been accorded vitamin D that is also critical in pregnant women and young children for instance because of its involvement in bone mineralization but also its more recently discovered immune-modulating function that is thought to prevent development of autoimmune diseases like diabetes mellitus type I. A healthy balanced diet provides the best basis for optimal pregnancy outcome, lactation performance, and complementary feeding. However, supplements or fortified foods may be needed to cover the high requirements especially of critical vitamins such as vitamin D and folic acid and to correct unfavorable dietary patterns in women or to adapt foods to the needs of young children.

Key words: vitamins, pregnancy, lactation, development, infants

Introduction

As the foundations for a healthy life are already laid in the womb and early infancy, adequate nutrition in this period is of great importance. With their numerous functions in the body, vitamins are essential for growth and development, and special requirements arise during pregnancy, lactation, and infancy. However, there is still a lack of concrete recommendations for these life phases due to a scarcity of direct studies in the respective population groups that is among other reasons ethically founded. Furthermore, assessment of vitamin status can be impeded by alterations in biomarkers. This is especially the case during pregnancy, when the physiological increase in blood volume causes a hemodilution leading to decreased plasma levels of certain vitamins while others are unaffected due to increases in carrier proteins [1]. A recent Danish study found that the reduction in serum cobalamin associated with pregnancy was

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accounted for by lower levels of haptocorrin-bound cobalamin while the biologically available form bound to transcobalamin was unchanged compared to non-pregnant women. Vitamin B_{12} absorption showed no alterations either [2].

Requirements and recommendations for intake

In the case of most vitamins, current recommended daily intake levels for pregnant and lactating women as well as older infants (6 months to two years of age) are extrapolated from those for non-pregnant women or older children, respectively, or derived from the composition of breast milk [3]. However, especially in the latter case, the wide individual variation of nutrient contents in breast milk has to be considered [4].

Accordingly, the recommended intake levels vary between different national nutrition entities. However, all recommend higher intake levels for vitamins in pregnancy and lactation apart from vitamin K and a few other exceptions in some countries (see Table I for some examples).

Vitamin A

Vitamin A is best known for its role in color and night vision, its aldehyde 11-cis retinal being an integral component of the photoreceptor pigment rhodopsin. According to WHO worldwide estimates in 2009, vitamin A deficiency affects about 190 and 19 million young children and pregnant women, respectively, mainly in the African and South-Asian regions. It is a major cause of xerophthalmia, night blindness, and anemia [5]. Moreover, it is essential for immune functions and mucosal integrity, and inadequate supply is associated with a higher susceptibility for intestinal and respiratory infections [6, 7]. Through its role in gene regulation, vitamin A is involved in fetal development, organogenesis, limb formation, and body symmetry. Upon binding the active form retinoic acid,

Table I: Recommended daily intake levels of some vitamins from selected nutrition and health organisations (references [16–19]). Changes compared to levels recommended for non–pregnant women are given in parentheses.

	Vitamin A µg/d	Vitamin D µg/d	Vitamin E mg/d	Vitamin K µg/d	Vitamin B1 mg/d	Vitamin B2 mg/d	Vitamin B6 mg/d	Vitamin B12 µg/d	Folate µg/d	Vitamin C mg/d
FAO/ WHO 2001										
Pregnancy	**800**	5	*	55	**1.4**	**1.4**	**1.9**	**2.6**	**600**	**55**
	(60)				(27)	(27)	(46)	(8)	(50)	(22)
Lactation	**850**	5	*	75–90	**1.5**	**1.6**	**2.0**	**2.8**	**500**	**70**
	(70)				(36)	(45)	(54)	(17)	(25)	(56)
IOM, 1998/2000/ 2001/2010										
Pregnancy	**750–770**	15	15	75–90	**1.4**	**1.4**	**1.9**	**2.6**	**600**	**80–85**
	(7–10)				(27–40)	(27–40)	(46–58)	(8)	(50)	(13–23)
Lactation	**1200–1300**	15	**19**	75–90	**1.4**	**1.6**	**2.0**	**2.8**	**500**	**115–120**
	(71–86)		(27)		(27–40)	(45–60)	(54–67)	(17)	(25)	(60–77)
D–A–CH, 2000 (2010)										
Pregnancy	**1100**	5/20#	**13**	60	**1.2**	**1.5**	**1.9**	**3.5**	**600**	**110**
	(37.5)		(8)		(20)	(25)	(58)	(17)	(50)	(10)
Lactation	**1500**	5/20#	**17**	60	**1.4**	**1.6**	**1.9**	**4.0**	**600**	**150**
	(53)		(42)		(40)	(33)	(58)	(33)	(50)	(50)
NNR, 2004										
Pregnancy	**800**	**10**	**10**	n.d.	**1.5**	**1.6**	**1.5**	2.0	**500**	**85**
	(14)	(33)	(25)		(36)	(23)	(15–25)		(25)	(13)
Lactation	**1100**	**10**	**11**	n.d.	**1.6**	**1.7**	**1.6**	**2.6**	**500**	**100**
	(57)	(33)	(37.5)		(45)	(31)	(23–33)	(30)	(25)	(33)

Bold: differing from levels for non-pregnant/non-lactating women
* no evidence for altered requirements
# revision of 2010 gives 20 µg/d for all population groups under the assumption of no sunlight exposure

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the nuclear retinoic acid receptors (RAR) and the retinoid X receptors (RXR) build heterodimers with each other and, in the case of RXR, also with other nuclear receptors like PPARs or vitamin D receptor, and act as ligand-activated transcription factors via retinoid acid response elements (RARE). During fetal development, they regulate cell differentiation through morphogenetic processes based on local concentration gradients [7]. Deficiency during pregnancy can thus result in teratogenic effects on various organs and tissues such as the heart, eyes, the circulatory, pulmonary, urogenitary and central nervous systems, especially the hindbrain. However, excessive exposure to vitamin A shows teratogenic effects as well, and both, deficiency as well as overload, lead to malformations like spina bifida, hydrocephalus, palate cleft, anophthalmia and limb deformities [8, 9].

Vitamin D

Vitamin D has received much attention over the last years, as new functions beyond its role in bone metabolism have emerged. Indeed, vitamin D receptor is expressed in many tissues of the body and inadequate status of 1,25-$(OH)_2$-cholecalciferol has been associated with higher risk for cardiovascular disease and certain cancers, insulin resistance and disturbed glucose metabolism. Vitamin D has immune-modulating effects and is a regulator of gene expression [10]. In early life, the role of vitamin in bone formation is obviously of great importance. As status in pregnant women is often suboptimal and not sufficient to assure adequate concentrations in breast milk, supplementation of infants with 10 μg/d is advised [11]. Another crucial role of vitamin D in early life is related to its role in directing the immune system towards a more tolerogenic behavior, by stimulating the differentiation of naive CD4+ T cells to regulatory T and T helper 2 cells, thus preventing the development of autoimmune diseases [12]. Indeed, a relationship between low 25-OH-D_3 status and the incidence of diabetes mellitus type 1, multiple sclerosis, and rheumatoid arthritis has been observed in epidemiologic studies [13]. In a Norwegian study, the odds of developing diabetes mellitus type 1 were more than twofold higher in children of mothers with the lowest 25-OH D_3 levels (≤ 54 nmol/L) compared to children of mothers with the highest levels (> 89 nmol/L) [14].

So far, intake recommendations for infants are mainly based on the needs for bone development and the avoidance of rickets while recently discovered functions of vitamin D have so far not been taken into account in light of the scarcity of scientific data [15–19].

Folate

Folate is among the first vitamins that come to mind in the context of pregnancy and fetal development due to its role in the prevention of neural tube defects (NTDs). Indeed, a reduction of the incidence of NTDs was the motivation to implement mandatory fortification of cereal products like flour or bread with folic acid in 72 countries worldwide, high- and low-income alike, especially on the American continent and in the Eastern Mediterranean region. This measure was accompanied by a notable decrease in the incidence of NTDs [20–22].

The main function of the various folate metabolites is the provision of single carbon (C1) units for the synthesis of purine and pyrimidine and amino acid metabolism. In this way, it is essential for DNA replication and the reconversion of homocysteine to methionine. However, as a major source of methyl groups, folate is also involved in epigenetic methylation reactions. Effects of maternal folate status on epigenetic patterns and the phenotype of the offspring have been reported [23].

Besides folate, vitamin B_2, B_6 and B_{12}, being cofactors of enzymes catalyzing C1 transfer reactions, are essential for growth and development [24].

Critical vitamins in pregnancy and infancy

The particular role of and higher requirement for certain vitamins in pregnancy and infancy make pregnant and lactating women and young children prone for deficiency states. Inadequate supply with vitamins in pregnancy and during lactation exhausts the mother's body stores. Indeed, consecutive pregnancies further deplete low status due to malnutrition with detrimental consequences for mother and fetus [25]. Maternal micronutrient status determines that of the infant allowing the build-up of stores during the first four to six months of life [26].

As mentioned above, at the global level, vitamin A is among the most critical nutrients, but less so in high-income countries [5]. In these latter, focus is rather on folate and vitamin D supply. A low intake of folate has repeatedly been reported as indeed consumption of its main sources, leafy green vegetables, pulses, wholegrain cereal, some fruits like citrus fruits, and liver, is insufficient.

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The Austrian Nutrition Report 2008 showed inadequate intake of vitamin D, folate and vitamin B_6 from food in the participating pregnant women across all age groups. A marginal intake was seen for vitamin B_2 in women aged less than 25 years. However, in a Viennese subsample, biochemical folate status was satisfactory in more than 70 % of the women and markedly low in less than 5 %. In turn, vitamin B_6 status assessed through the activation of erythrocyte glutamate oxaloacetate transaminase (EGOT) was insufficient in about 85 % with markedly low levels in 25 %. Vitamin D status was marginally low in about 30 % [27].

In the German National Health Interview and Examination Survey for Children and Adolescents (KiGGS), 69 and about 64 % of non-immigrant boys and girls aged 1–2 years, respectively, had sufficient vitamin D status (> 50 nmol/L), moderate and severe deficiency were found in about 7 and 0.5 % of boys, respectively, and in 6 and 1.3 % of girls. Deficiency was more common in children from immigrant families, especially in girls [28].

Improving vitamin supply in early life

As outlined before, optimal vitamin supply is particularly important during early life as it lays the foundations of a future health and wellbeing. Measures to improve vitamin intake in pregnancy and infancy therefore deserve high priority in public health.

Generally, pregnancy has been shown as a period of greater health awareness in women making them more amenable to lifestyle and diet changes [29]. However, considering the increased requirements for vitamins during pregnancy and the difficulties often seen with the implementation of dietary changes, supplementation of critical nutrients presents a convenient approach to ensure adequate supply. In the Austrian Nutrition Report 2003, use of nutritional supplements was reported by 89 % of pregnant women between the 21st and 30th gestational week and 94 % between the 31st and 40th. In both groups, multivitamin products were most used [30]. Intake of folic acid supplements, either alone or in combination with other nutrients, was associated with a better status of B vitamins (B_2, B_6, B_{12}, folate) in Norwegian pregnant women [31]. Supplements contribute notably to vitamin D intake in pregnancy although the proportion of women not meeting the recommended intake level remains high even among supplement users. In turn, other vitamins might be supplied in excess through supplements so that careful administration is warranted [32].

Fortified foods are another source of vitamins during pregnancy and lactation especially if women are not willing or able to take supplements as evidenced in the case of folate [20]. They are of particular relevance in low-income countries and women with low socio-economic status [33].

Fortified foods are also a major source of vitamins in infants and toddlers. In the former, infant formula supplies the increasing nutrient requirements no longer met by exclusive breastfeeding. In turn, as toddlers are gradually fed regular foods, a careful selection has to assure adequate vitamin intake. A US survey revealed a high contribution of fortified foods to vitamin supply in toddlers suggesting unfavorable dietary patterns such as a low vegetable intake often reported in toddlers [34–35]. In accordance with these findings, in German children aged 1 year, mean folate intake was below the age-specific recommended intake level. Consumption of fortified foods, particularly infant formula and weaning foods as well as breakfast cereals, was associated with higher folate intake [36].

Conclusion

Adequate vitamin status is a prerequisite for healthy development in early life that also influences adult health and wellbeing. A healthy balanced diet during pregnancy, lactation, and infancy is the best source of these essential nutrients making nutritional counseling for pregnant women and mothers a public health priority. However, supplementation and/or fortification can make a contribution when the high demands for growth and development are difficult to meet through food alone.

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