Nutritional Deficiency & Impact on Health

Chapter 5

Micronutrients Deficiencies in Early Life and Impact on Long-term Health

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Abstract

Nutrition in early life is of extreme important due to direct correlation with long-term increased risk of non-communicable diseases (NCDs). The fetal and postnatal level of micronutrients and polyunsaturated fatty acids (PUFAs) may alter metabolism, organ growth, development and function leading to increased risk of cardio metabolic diseases, obesity, renal disorders, respiratory disorders, metabolic syndrome, and, eventually to type 2 diabetes and cardiovascular diseases. This chapter is focused on the complexed effects of micronutrients (vitamins and minerals) and PUFAs deficiencies on the health and discuss the importance of supplementation and education programs as a health policy strategy.

Keywords: Micronutrients deficiencies; PUFAs (polyunsaturated fatty acids) deficiencies; Early life nutrition; Long-term health; Nutrition literacy.

1. Introduction

The intake of suitable macronutrient and the impact on growth and development as well on wellness is well-known. It is sustained by a balanced and diversified diet. Nevertheless, the adequate fetal and postnatal intake of vitamins could impact significantly early life and long-term effects on predisposition to several health outcomes (**Figure 1**).

VITAMINS	COMMON FOOD SOURCES	MEDICAL IMPLICATIONS OF DEFICIENCY
Water-soluble vitamins		
Vitamin B_1 (thiamine)	Enriched cereals and breads; unrefined grain; pork; legumes, seeds nuts	**Beri-beri**: Edema, anorexia, weight loss; apathy, decrease in short-term memory, confusion; irritability; muscle weakness; an enlarged heart
Vitamin B_2 (riboflavin)	Dairy products, fortified cereals, meats, poultry, fish, legumes	**Ariboflavinosis**: Sore throat, hyperemia, edema of oral mucosal membranes, cheilosis, angular stomatitis, glossitis, magenta tongue, seborrheic dermatitis, normochromic normocytic anemia
Vitamin B_3 (niacin)	Meat: chicken, beef, fish; enriched cereals or whole grains; most foods	**Pellagra**: Pigmented rush in areas exposed to sunlight; vomiting; constipation or diarrhea; bright red tongue; neurologic symptoms.
Vitamin B_5 (pantothenic acid)	Wide distributions in foods, especially animal tissues; whole grain cereals; legumes	Irritability and restlessness, fatigue, apathy, malaise, gastrointestinal symptoms, neurological symptoms
Vitamin B_6 (pyridoxine)	Chicken, fish, pork, eggs, fortified cereals, un-milled rice, oats, starchy vegetables, non-citrus fruits; peanuts, walnuts	Seborrheic dermatitis, microcytic anemia, epileptiform convulsions, depression and confusion
Vitamin B_7 (biotin)	Liver Egg yolk	Conjunctivitis; central nervous system abnormalities, glossitis, alopecia, dry, scaly dermatitis
Vitamin B_9 (folic acid)	Citrus fruits, dark green vegetables, fortified cereals and breads, legumes	Impaired cell division and grown; **megaloblastic anemia**, neural tubes defects
Vitamin B_{12} (cobalamin)	Animal products, fortified cereals	**Megaloblastic anemia,** neurologic symptoms
Vitamin C	Citrus fruits, potatoes, peppers, broccoli, spinach, strawberries	**Scurvy**, defective collagen formation leading to subcutaneous hemorrhage; aching bones, joints, and muscle in adults, rigid position and pain in infants
Fat-soluble vitamins		
Vitamin A	Carrots; dark green and leafy vegetables, sweet potatoes and squash, broccoli	Night blindness; **xerophthalmia**; keratinisation of epithelium in gastro-intestinal system; respiratory and genitourinary tract, skin becomes dry and scaly
Vitamin D	Fortified milk; exposure of skin to sunlight	**Rickets** in children; inadequate bone mineralization (osteomalacia)
Vitamin E	Vegetable oils, margarine; wheat germ; nuts, green leafy vegetables	Muscular dystrophy, neurologic abnormalities
Vitamin K	Green leafy vegetables; cabbage family bacterial flora of intestine	Defective blood coagulation, hemorrhagic anemia of newborn

Figure 1: Synthesis of vitamins, common food sources and medical implications [1-7].

Whole blood collected on an anticoagulant substance can be separated by centrifugation into blood plasma and cells.

About 10% of blood plasma are solutes, of which: a) about 70% are plasma proteins; b) 30% are: small organic molecules, inorganic salts, and many other substances that even in small amounts are essentials: enzymes, hormones, other metabolites, and important nutrients as vitamins and trace elements (**Figure 2**).

Measurements of the concentrations of components in blood plasma are very important in the diagnosis and treatment of many diseases, and should be a current diagnosis paraclinical test that help on patient management.

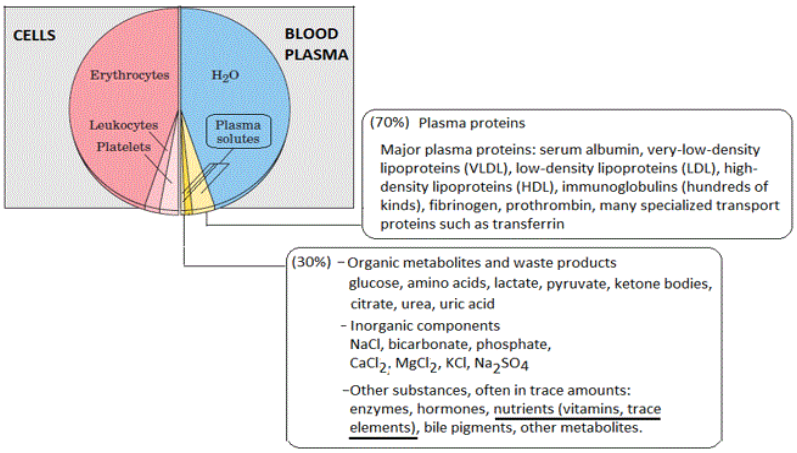

Figure 2: The composition of blood; vitamins and trace elements in a quantitative representation (modified after Lehninger Principles of Biochemistry).

2. Deficiencies of Vitamins Fetal and Neonatal

2.1. Deficiencies of vitamin B complex (Oana Lelia Pop)

B vitamins play a critical role in maintaining a proper function of the human body that is transposed into good health and well-being. Directly affected by the levels of B vitamins are processes as: energy delivery, intellectual functions, and cell metabolism. The presence of the vitamin B complex in fetal and postnatal life gives it an important role, especially in the nourishment of the premature neonates [8]. **Figure 3** shows the vitamin B complex and some natural sources, with their content in 100 g edible portion of food. The fetus feeds from the mother through the umbilical cord after being filtered through the placenta, so the mother's diet and her stocks in B vitamins are essential nutrients [9]. Furthermore, health authorities, including the World Health Organization (WHO), endorse breastfeeding exclusively for six months [10]. The role of vitamin B complex in the normal growth of the fetus and the newborn baby is more or less defined in the scientific papers. The growth and evolution of babies are influenced by the presence of the correct dosage of B vitamins in their diet [11].

Thiamin, or B1, is acting as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. This vitamin is important in maintenance of nerve membrane

function, and the synthesis of myelin and several types of neurotransmitters (acetylcholine, serotonin, and amino acids). Deficiencies in B1 vitamin is linked to beriberi disease. This disease was registered in infants at 3 to 4 weeks of age from mothers with beriberi. Table 1 offers the recommended adequate intake (AI) for babies breastfed (up to 6 months), babies from 7 to 12 months, and for the pregnant woman.

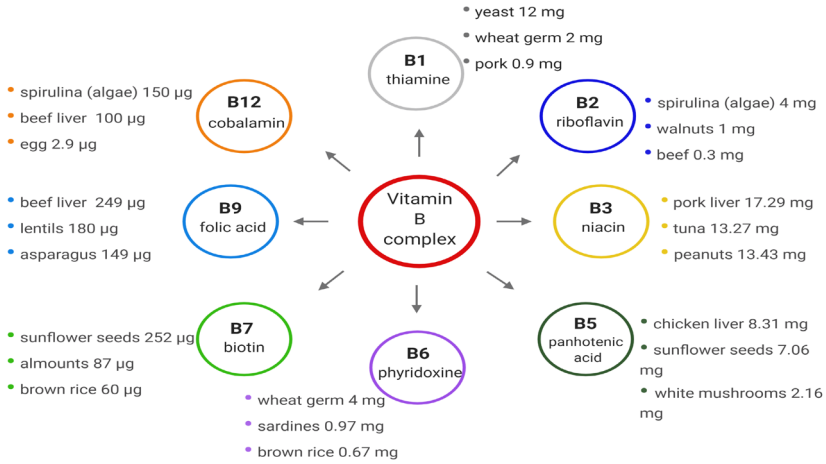

Figure 3: Vitamin B complex and food sources per 100 g.

Thus, only a well-nurtured mother will be able to ensure the B1 vitamin amount needed for her infant [12]. No significant differences were observed in the milk of lactating women with thiamine supplements and lactating well-nourished mothers [13].

The determination of B2 vitamin or riboflavin AI was established having in mind the correlation between this vitamin amount in human milk and the milk daily intake. Because most plant and animal-based foods contain at least small amounts of riboflavin [14] covering the AI, the estimated average requirements (EAR) is not a great issue for the lactating mothers and food feed babies (7-12 months). Folate (B9), niacin (B3), riboflavin (B2), pyridoxine (B6) and B12 (cobalamin) correlated with zinc ingestion are involved in carbon metabolism. Based on these, B complex are important in early gestation for early cell proliferation, growth, and protein synthesis [15]. Signs of different deficiencies in infants can be seen during pregnancy. Fetal resorption was observed in rats and mice with riboflavin deficiency, without a relevant correlation to humans. Recurrent cleft lip and cleft palate in siblings were associated with riboflavin, vitamin A and folic acid (B9) deficiencies [16].

B5 vitamin is an essential nutrient for humans, necessary for the biosynthesis of coenzyme A, which is needed in a vast range of biological processes, such as fatty acids metabolism [17].

Correlations between the newborn initial weight loss, the rate of return to the birth weight, and the weight at discharge are done in correlation with pyridoxine or vitamin B6. The most common clinical symptoms of B6 deficiency are seborrheic dermatitis, microcytic ane-

mia, epileptiform convulsions, and depression, facts that can affect the mother and the infant as well [13].

Mammals obtain B7 or biotin from food products (registering low amounts in fruits and high amounts in animal organs) or from gut bacteria. Deficiency in biotin for infants and pregnant women are rarely reported. Results showed that diet supplementation with10 mg/day of biotin during the ninth month of pregnancy induce no adverse effects to the mother or infant [11].

The folic acid (B9 vitamin) deficiency is correlated with the coexisting iron or vitamin B12 in an adequate amount. During pregnancy, folate requirements are higher due to the intense cell division and metabolism related to placental and fetal evolution, uterine expansion, and maternal blood volume enlargement. Women of delivering age, i.e., those becoming pregnant, and pregnant women in the first trimester are recommended to increase the folic acid intake per day from supplements. This recommendation is associated with effective action in neural tube defects risk reduction [18,19].

Vitamin B12 or cobalamin, together with folate, are mandatory cofactors in the synthesis of RNA and DNA. Cobalamin is needed for maintaining the nervous system functionality. Therefore, cobalamin is critical to the development during the early years of life [20,21]. Cobalamin stock in utero is an important determinant of cobalamin status in the newborn and during infancy, and there is an effective connection between maternal and newborn cobalamin status. Still, little data exist regarding the relationship between maternal factors influence infant vitamin status after the newborn period or how newborn folate and cobalamin status is related to the situation later in infancy and childhood [22].

Tabel 1: Dietary Reference Intakes for the vitamin B complex for pregnant woman and for infants of 0-6 months and 7-12 months [23].

B vitamin	Pregnant women		0-6 months infant AI***	7-12 months infant AI***
	EAR*	RDA**		
B_1 thiamine	1.2 mg/day	1.4 mg/day	0.2 mg/day	0.3 mg/day
B_2 riboflavin	1.2 mg/day	1.4 mg/day	0.3 mg/day	0.4 mg/day
B_3 niacin	14 mg/day	18 mg/day	2 mg/day	4 mg/day
B_5 pantothenic acid	6 mg/day***	-	1.7 mg/day	1.8 mg/day
B_6 pyridoxine	1.6 mg/day	1.9 mg/day	0.1 mg/day	0.3 mg/day
B_7 biotin	30 µg/day***	-	5 µg/day	6 µg/day
B_9 folate	520 µg/day	600 µg/day	65 µg/day	80 µg/day
B_{12} cobalamin	2.2 µg /day	2.6 µg /day	0.4 µg/day	0.5 µg/day

*EAR - estimated average requirements; ***AI- adequate intake

Studies regarding the deficiencies in early life and impact on the long-term health of most of the B vitamins are limited, with fluctuations regarding folate and cobalamin, which are

the most studied. Thus, close awareness should be given to the identification of indicators on which to base B complex supplementation. Nearly all of the B complex vitamin deficiencies are, in most cases, reversible and can be recovered in days up to 2-3 years (i.e. B12). However, because of their role in critical deficiency illnesses such as pellagra (a lack of niacin) and anemia (riboflavin and other B vitamins), as well as skin and mouth lesions, these B vitamin complex are added to breakfast designated cereals, to milk formula and supplementary foods. B vitamin requirements can easily recovered with adequate and equilibrate nutrition when no other genetic or malabsorption illnesses are correlated or special diets adopted (i.e. vegan).

2.2. Deficiencies of Biotin (Romana Vulturar)

Biotin (vitamin H /vitamin B7) is a water-soluble vitamin and has a key role in energy metabolism and regulation of oxidative stress, being a crucial cofactor for five carboxylases involved in gluconeogenesis, fatty acid and amino acid metabolism [24,25]. New evidence shows a vital role of biotin in chromatin structure, gene expression and genome stability [24,26,27].

Mammals obtain biotin from food (egg yolk, liver, wheat, oats, spinach, mushrooms, rice), or from gut bacteria [24, 26,27].

Causes of biotin deficiency (BD):

1. Genetics [2, 3]: few Inborn Errors of Metabolism (IEM) due to enzyme deficiencies: holocarboxylase synthetase or biotinidase, that if untreated give severe BD. Biotinidase screening should be part of the workup of newborns/children showing clinical features, and the clinicians should follow these patients, takes months to reverse the symptoms, but with good compliance, the outcomes are good.

2. Acquired [2, 3, 24, 27, 28]:

a. Severely malnourished children in developing countries and through the intake of modified milk without biotin supplementation;

b. Alteration in microbiota due to broad-spectrum-antibiotics treatment or inflammatory bowel disease,

c. Drug-vitamin interaction: patients receiving antiepileptics (carbamazepine, valproate, phenytoin, phenobarbital) or isotretinoin for acne treatment, or parenteral nutrition; biotin requirements may increase during these therapies.

d. Elderly, smokers, excessive consumption of alcohol, consumption of large amounts of raw egg whites (avidin binds biotin) reduces biotin absorption.

e. Marginal BD is common in pregnancy (about half of the pregnant women in USA); the negative statistically significant correlation between hyperemesis gravidarum severity and serum biotin levels was noted. Likewise, lactation can lead to an increased demand for biotin.

Regarding the pathophysiology of BD, this can leads to several abnormalities, mainly dermal and neurological dysfunctions. Biotin regulates immunological and inflammatory functions, playing a key role in the function of natural killer lymphocytes, in B- and T-cell immunity. In BD there are increasing levels of IL-1-beta and proinflammatory cytokines TNF-alpha [24,25].

Dermal abnormalities: hair loss (alopecia) and periorificial (eyes, nose, mouth) dermatitis with a scaly, red rash similar to that of zinc deficiency. Patients may also develop conjunctivitis and skin infections [2,29].

Neurological symptoms: hypotonia, seizures, ataxia, mental retardation, numbness of the extremities, and developmental delay in children. The patient may also show depression, lethargy, a history of hallucinations, ketolactic acidosis, organic aciduria. Initial clinical symptoms of acquired BD include gradual hair loss, dry skin, lesions on the feet and legs. Infants may initially show mild scaly dermatitis on the face similar to soaps-dermatitis-rash. In adults (after a few weeks of having a raw-egg-diet) desquamative dermatitis, anorexia, lethargy, hyperaesthesia are observed; in these cases, administration of biotin relieved symptoms in five days. Individuals with hereditary disorders of BD may show impaired immune function with increased susceptibility to candidiasis. Biotinidase deficiency typically shows symptoms between the age of one week to more than one year and may associates hearing loss, optic atrophy [3,26].

For treatment/ management, oral biotin supplements have high bioavailability, and patients usually respond well to large doses of biotin (5 mg/day regardless of the etiology of BD). Early intervention with lifelong biotin doses (5-20 mg/day) can treat/prevent clinical signs of biotinidase deficiency; failure to manage biotinidase deficiency at an early stage can cause irreversible neurodevelopmental delay and autistic behavior [3,26,30].

The differential diagnosis: a) sodium-dependent multivitamin transporter defect, that is another IEM [31], b) acrodermatitis enteropathica (given by disorders in zinc metabolism) [27].

Regarding the fetal development, evidence shows that lack of biotin is teratogenic in animal models (malformations: mainly cleft palate, micrognathia, micromelia) [26,27,32].

2.3. Deficiencies of Folic acid (Adriana Fodor)

Folate is a water-soluble B vitamin that occurs naturally in food. Folic acid is the synthetic form, with increased bioavailability, used for food fortification and in supplements.

Folates function as cofactors within C1 metabolism, required for DNA and RNA biosynthesis, amino acid and lipids metabolism and methylation processes. Thus, folate deficiency will affect more the cells that rapidly divide, including the progenitors of red blood cells, thereby producing megaloblastic anemia (immature, enlarged blood cells), other bone marrow cells, leading to leukopenia and thrombocytopenia or fetal cells, leading to low birth weight, preterm delivery and fetal growth retardation.

During embryogenesis, the neural tube has increased need of folate for cell differentiation, growth, and closure to form the spinal cord and brain. Folate deficiency during the periconceptional period can induce neural tube defects (NTDs), which are the most frequent human malformations occurring during pregnancy. Conclusive evidence from randomized controlled trials has shown that folic acid supplementation in the periconceptional period unequivocally reduces the occurrence of NTDs, and significantly reduces the risk for other congenital malformations like heart defects and orofacial clefts. For the prevention of NTDs, women are recommended to take 400 μg/d folic acid as a supplement from preconception until the end of the first trimester of pregnancy [33]. However, the evidence suggests that the current recommendations are largely ineffective because of the poor compliance of women with folic acid supplementation as recommended before and in early pregnancy [34]. In contrast, when mandatory folic acid fortification is undertaken widely on population, it results in marked reductions in NTDs and very low rates of anemia secondary to folate deficiency [35]. Over eighty countries worldwide to date (including the USA, Canada and Australia) have regulations for the mandatory fortification of staple foods with folic acid in order to prevent NTDs.

As folate is required for the re-methylation of homocysteine to methionine, a typical consequence of folate deficiency is an elevation in plasma homocysteine, which, in turn, is implicated in the etiology of cardiovascular diseases [36].

Emerging evidence from candidate gene approach studies links maternal folate during pregnancy with DNA methylation in offspring genes involved in neurodevelopment and cognitive function in childhood [37]. One randomized trial to date has shown that folic acid supplementation in pregnancy led to significant changes in DNA methylation in genes related to brain development, IGF2 and BDNF [38].

Apart from maternal folate status during pregnancy, the child's folate status also seems to impact health. A prospective cohort study in 2922 children has shown that high dietary intake of folic acid at the age of 1 year was associated with a lower body weight at the age of 6 years [39].

2.4. Deficiencies of vitamin C (Angela Cozma)

Vitamin C, also known as ascorbic acid (AsA) is recognized as a vital dietary micronutrient based on its ability to prevent scurvy in humans. While this condition is rare in the Western world, AsA deficiency, defined by a plasma concentration < 23 μmol/l, is surprisingly common [40].

AsA plays a major role in defense against increased oxidative stress during pregnancy [41]. AsA levels decrease during pregnancy, due to physiological changes in pregnancy and inadequate intake [42]. Pregnancy is associated with increased susceptibility to oxidative stress. The antioxidant deficiencies during pregnancy and placental oxidant-antioxidant imbalance may affect the development of the fetoplacental unit or the eventual offspring [43]. There are many studies regarding AsA deficiency during pregnancy and low birth weight and preterm delivery [44-46].

The increased consumption of fruit and vegetables, an excellent source of AsA, during pregnancy has been shown to be positively associated with birth weight [47,48].

Consistent findings from experimental animal models of both AsA depletion and deficiency have suggested that AsA -is playing a crucial role in the brain, particularly during development [49-51].

In humans, studies have shown that poor maternal AsA status results in increased fetal oxidative stress, impaired implantation and increased risk of complications including pre-eclampsia [52-54]. Women with pre-eclampsia have been shown to have reduced levels of AsA and several studies have investigated a potential effect of AsA supplementation [55]. It is not clear to what extent AsA supplementation may ameliorate this risk.

Recently, Takeshita examined the effect of AsA deficiency on the concentration of tetrahydrobiopterin (BH_4) using ODS rats, which are defective in the gene for AsA synthesis. AsA deficiency determines a decrease in the monoamine levels in the brain and plays an important role in the pathophysiology of neuropsychiatric and cardiovascular disorders through alteration in BH_4 metabolism [56].

On the other hand, it has been shown that AsA modulates ten-eleven translocation (TET) activity, an enzyme with a role in DNA demethylation. DiTroia has shown that maternal AsA is required for proper DNA demethylation, and the development of female fetal germ cells in a mouse model with AsA deficiency leads to an aberrant DNA methylation. Maternal AsA deficiency does not affect overall embryonic development but leads to reduced numbers of germ cells, delayed meiosis and reduced fecundity in adult offspring. The author concludes that deficiency in AsA during gestation partially recapitulates loss of TET1, and provide a

potential intergenerational mechanism for adjusting fecundity to environmental conditions [57].

2.5. Deficiencies of vitamin A (Adina Chiș)

Vitamin A (all-trans-retinol) deficiency (VAD) is a major health issue worldwide, especially in low/middle-income countries; risk groups for VAD have been identified even in developed countries [58]. The VAD may have serious consequences at any age; when it appears during pregnancy and early childhood, the consequences can be severe for maternal health, but mainly for the fetus.

Low intake of vitamin A, especially during the third quarter of pregnancy, can lead to fetal skeleton malformations, impairments in the ocular and immune fetal systems development; in more severe cases of maternal deprivation, premature birth or even fetus death can occur [59,60].

Without fully understanding the pathophysiology, studies have shown that in neonate fed with low-vitamin A milk, the immune system is affected: an increased risk for respiratory tract infections and complications during viral infections (measles) can occur.

During the childhood, the VAD is associated with xerophthalmia that, untreated, can progress to nyctalopia; later in life, if this deficiency is untreated will affect: cell differentiation, growth and reproduction, will increase the risk of infection and, even the mortality [58].

Furthermore, animal studies support the involvement of VAD in the pathogenesis of certain diseases; depending on the severity of VAD, were observed anomalies in the development of eyes, brain, kidneys, lungs, and may cause even death and fetus resorption. There are also studies that have shown that the VAD during the pregnancy was associated with the development of diabetes later in life [4, 58]

2.6. Deficiencies of vitamin D3 (Adela Viviana Sitar Tãut)

Vitamin D deficiency (VDD) represents a public health problem, being observed worldwide in pregnant women and their newborns [5, 61]. An important proportion of pregnant women (prevalence ranged 18-84%) [5, 6, 62, 63], respectively of newborns [6] presents VDD. According to the most experts, vitamin D deficiency is defined as a 25-hydroxyvitamin D level less than 20 ng/ml [5, 64], but increased values are recommended by Endocrine Society during pregnancy (at least 30 mg/ml) [5]. Many studies showed a positive correlation between maternal and fetus/newborn's vitamin D levels [61], the fetus being dependent on maternal D vitamin level [62,65] (**Table 2**).

Risk factors in developing vitamin D deficiency are extremely various; there are

mentioned causes like receiving insufficient vitamins [63], low intake of fortified food and low compliance of supplementation [63], black race [6], body covering [63], winter birth [6] living in cold climates or northern latitudes [66,67], inadequate sunlight exposure [5], maternal deficiency in relationship or not with diet (vegetarians) [5,6,66], maternal obesity [6, 68] (**Table 2**).

Recent studies have shown that vitamin D deficiency has a major impact not just only on skeletal development and bone mineralization [5,6,62,63,65,69,70], but also being associated with a broader range of adverse infant and maternal health outcomes (on a short and long time) [5,6,71] (**Table 2**).

Table 2: Vitamin D Deficiency

At maternal level determines:	**References**
infertility or implantation failure	[5, 72, 73]
increased risks of primary cesarean delivery	[74, 75]
preterm delivery	[61, 62, 76]
recurrent pregnancy loss (vitamin D inhibits pro-rejection cytokines and favor the release of tolerance-promoting cytokines, down-regulate TNF-α, IL-6, and IL-10 at placental level)	[5, 77, 78, 79]
bacterial vaginosis (insufficient antimicrobial peptide cathelicidin synthesis)	[5, 62, 63, 65, 66, 75, 80]
risk of pre-eclampsia (vitamin D influences over RAAS system, over antiangiogenic factors like FMS-like tyrosine kinase-1 and vascular endothelial growth factor, also controlling fetal-placental immune responses)	[5, 62, 63, 66, 68, 75-77, 81, 82]
risk of gestational diabetes mellitus (vitamin D has positive effects - increase insulin sensitivity and regulate insulin production)	[5, 62, 63, 66, 67, 75-77, 82-86]
risk of postpartum depression, periodontal disease	[75]
Intrauterine determines:	
intrauterine growth restriction	[5, 62, 66, 75-77]
low birth weight, length	[61-63 66, 71, 87]
head circumference	[66]
increased risk of small-for-gestational-age	[7, 62, 71]
development of rickets, skeletal deformities	[7, 63]
increased risk of premature or later in life fracture (abnormality in calcium and phosphate metabolism)	[62, 75, 88, 89]
pelvic deformity	[5, 7, 75]
alteration of the immune system with an increased risk of lower respiratory tract infections, early-onset neonatal sepsis (deficiency is associated with dysregulation of cytokines and immunomodulation)	[62, 63, 69, 75, 90, 91, 92]
decrease induction capacity of antimicrobial peptides - cathelicidin (LL37), beta-2 and beta-3 defensins	[90]
decrease of T helper cells 2 (Th2) differentiation	[90]
altered monocyte and macrophages' response	[92]
diminished activity against bacterial and viral agents	[92]
improper local control of pathogens	[90]

impaired fetal and childhood growth and development - slower than normal - of the neonatal cardiovascular system, brain	[5, 70, 76]
lung development	[76, 93, 94]
multiple neonatal respiratory disorders - acute lower respiratory tract infections, transient tachypnea of the newborn, respiratory distress syndrome, bronchopulmonary dysplasia	[5, 62, 94]
vitamin D upregulating some genes involved in lung development – matrix metallopeptidase 9, NF-k light polypeptide gene enhancer in B cells inhibitor, epidermal growth factor receptor, E1A binding protein p300. Also, vitamin D influences alveolar epithelial-mesenchymal interactions	[87, 93]
lipofibroblast proliferation, apoptosis of lung fibroblasts	[94]
increases surfactant synthesis	[87, 91]
the deficit of vitamin D is associated with changes in lung structure and function that can persist into later life	[68, 69, 91, 93, 95]
high neonatal mortality	[61]
susceptibility for later-life diseases - metabolic syndrome, childhood adiposity and obesity, type 1 diabetes or even cardiovascular diseases	[5, 7, 62, 65, 70, 71, 82, 89, 96, 97]
vitamin D deficiency has the potential to program long-term vulnerability to cardiovascular disease (upregulating the renin-angiotensin system, altering normal proliferation and differentiation in the fetal heart, determining hyperplastic cardiomyocyte growth, affecting normal cardiogenesis)	[98, 99]
several case reports of vitamin D deficiency or rickets-associated pediatric cardiomyopathies or congenital heart diseases in offsprings in compromised maternal vitamin D	[99]
possible development of asthma, allergic rhinitis, eczema (in relationship with interaction between vitamin D and developing immune system)	[7, 62, 65, 68, 69, 75, 76, 82, 93, 100, 101, 102]
risk of psychiatric and neurological diseases – VDD can cause abnormal changes in brain morphology and development, possible reductions of neurotrophic factors, nerve growth factors, neuronal differentiation, axonal connectivity	[5, 68, 76]
involved in: -cellular proliferation, differentiation, neurotransmission and neuroprotection - DNA repair mechanisms - “serotonin paradox” - having anti-inflammatory effects, reducing cytokine associated with cognitive impairment levels	 [67] [67] [67, 103] [67, 104, 105, 106]
deficiency can be responsible for: - seizures or tetany development (due to hypocalcemia) - can play a role in autism or ADHD spectrum disorders - predisposition to schizophrenia, depression or multiple sclerosis	 [5, 7, 61, 62, 75, 107] [76, 108, 109, 110, 111] [5, 7, 62, 112, 113]
association between prenatal vitamin D status and global IQ or cognitive development with inconclusive results till now	[76, 114]
risk of retinopathy of prematurity development, being imply the lack of endothelial cells proliferation and angiogenesis’ inhibition by vitamin D (via thrombospondin)	
pediatric oncology patients, the deficit of vitamin D being frequently met in oncology patients. Future studies are needed to examine causality, to evaluate the frequency of vitamin D receptor (VDR) polymorphisms in children diagnosed with cancer, to establish the real temporal relationship between vitamin D deficiency and cancer	[116]

2.7. Deficiencies of vitamin E (Olga Orãșan)

The vitamin E (or alpha-tocopherol) is found in a variety of tissues, being lipid-soluble, and taken up by the body in a wide variety of ways. The content of alpha-tocopherol in the body of the fetus remains at 3-7 mg/kg throughout gestation [117].

Several genetic disorders lead to vitamin E deficiency, including:

- Mutations in the gene encoding hepatic alpha-tocopherol transfer protein, with symptoms similar to Friedreich ataxia [118-122].
- Abetalipoproteinemia, due to mutations in the microsomal triglyceride transfer protein associated with very low or absent levels of low-density lipoprotein and fat-soluble vitamin deficiencies. Symptoms include progressive ataxia, sensory-motor neuropathy, and vision impairment with retinitis pigmentosa.

In premature infants, vitamin E deficiency may cause a hemolytic anemia. Congenital hemolytic disorders such as thalassemia, sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, and spherocytosis may be associated with low vitamin E plasma levels [123-126].

In preterm infants, lack of vitamin E intake or fat malabsorption results in edema, thrombocytosis and hemolytic anemia and could eventually result in spinocerebellar degeneration. A tocopherol/total lipid ratio of greater than 0.8mg/g has been recommended to evaluate vitamin E sufficiency [117].

The amount of vitamin E in colostrum and preterm milk is two to three times higher than in mature milk. Formulas for preterm infants should contain at least one IU of vitamin E/g of linoleic acid, 0.6mg of d-alpha-tocopherol and 0.7IU/100kcal [117].

2.8. Deficiencies of vitamin K (Romana Vulturar)

Vitamin K corresponds to a group of fat-soluble compounds and their implication in health is related to vitamin K-dependent-proteins involved in [127-129]:

- **coagulation** (clotting factors II, VII, IX, X);
- **cardiovascular** system (decreased levels of vitamin K subtypes give arterial calcification)
- **bone development** (osteocalcin, matrix GLA proteins).

The vitamin K1 is predominantly from leafy greens and vegetables, while the main sources of Vitamin K2 are intestinal flora and fermented foods [128].

Vitamin K deficiency is rare in adults (malabsorption syndromes, or those treated with drugs that interfere with vitamin K) [128, 130]. Regarding the newborns, all have reduced Vitamin K at birth (low levels transferred across the placenta and low levels in breast milk).

Vitamin K Deficiency Bleeding (VKDB) is a potentially devastating consequence of vitamin K deficiency in newborns (**Table 3**).

Table 3: Vitamin K deficiency in newborns.

Based on the *causes*	**References**
• Hereditary-Combined-Vitamin-K-dependent-Clotting-Factors-Deficiency (VKCFD) is extremely rare - genetic recessive disorders with decreased activity of K-dependent proteins. With vitamin K supplementation: good prognosis. • Inadequate uptake or secondary to chronic disorders. • Context that is drug-related.	[131]
Based on the *timing of the presentation*	
• **Early VKDB** (within 24 h) - when mothers take vitamin K interfering substances (i.e. anticonvulsants); incidence without vitamin K-supplementation has been reported as 12%. • **Classic VKDB** (within the first week) is as a bleeding disorder; in combination with sepsis-induced-bleeding, has 62% fatality rate. Without Vitamin K supplementation, the current incidence is 0.25-1.7%. • **Late VKDB** (between one to twelve weeks) has the worse prognosis, and occurs in 4.4-72 infants /100, 000 births (increased risk in exclusively breastfed infants). 50% of these cases present intracranial hemorrhage (mortality rate is 20-50%).	[127, 132, 133, 134]

Vitamin K prophylaxis in newborns: within an hour of birth to prevent severe bleeding - an intramuscular injection or repeated oral doses for a minimum of 6 weeks [127,133].

3. Deficiencies of Minerals (Doina Miere, Lorena Filip, Simona C. Hegheș and Anamaria Cozma-Petruț).

3.1 Deficiencies of Calcium and Magnesium

Calcium (Ca) is essential for both fetal and postnatal bone development. In addition, it is involved in cell membrane functions, blood coagulation, enzyme and hormone actions, muscle contraction and nerve impulse transmission [135]. Physiological adaptations in maternal Ca homeostasis occur during pregnancy to meet the increased demand, but they appear to be independent of maternal Ca supply in populations with adequate Ca intake [136]. Thus, gestational Ca deficiency is rare in Western societies but has been described in low-income countries that have poor nutrition. Hypocalcemia in pregnancy has been linked with pre-eclampsia and intrauterine growth restriction (IUGR) [137]. Furthermore, an association has been suggested between maternal pregnancy-related hypertension and elevated blood pressure among offspring during childhood, adolescence and adulthood [138].

Magnesium (Mg) acts as a co-factor for numerous enzymes and plays an important role in various metabolic processes, neuronal and muscular excitability and vasomotor

tone modulation, respectively. Hypomagnesemia during gestation has been associated with hypertensive conditions, preterm delivery and low birth weight [139]. Moreover, intrauterine Mg deficiency has been postulated to alter organ structure and predispose the offspring to metabolic syndrome in later life [140].

The risk of Ca and Mg deficiencies is low in term breast-fed infants in the first six months of life [141] . In contrast, in 6 to 23-month-old children, inadequate complementary feeding has been associated with severe Ca and Mg deficiencies in developing countries. Ca deficiency affects bone mineralization and, consequently, linear growth. Mg deficiency results in anorexia and may indirectly contribute to growth retardation. Linear growth failure not only results in morbidity and mortality but also increases the risk of dyslipidemia, hypertension, and glucose intolerance in later life [142].

3.2. Deficiencies of Zinc

Zinc (Zn) is an essential mineral that plays a key role in cell growth, development, and differentiation having many biological functions including protein synthesis, cellular division and nucleic acid metabolism. Periods of rapid growth such as late pregnancy, infancy and puberty are more vulnerable to zinc deficiency. There are no specialized zinc storage systems in the body. Therefore, a compromised status can develop rapidly and is more common when the main staple foods are high in phytates, or people are following a vegetarian diet or are poorly nourished. Severe zinc deficiency is considered to be rare, while mild or moderate zinc deficiency seems to be more common [143].

It is estimated that 82% of pregnant women worldwide have a zinc intake lower than the recommended dietary intake, and the values may be even higher in developing countries [143]. Even if several earlier reports have shown that maternal zinc deficiency during pregnancy in humans is linked with various adverse pregnant outcomes, recent systematic reviews [144-146] demonstrate that zinc supplementation during pregnancy may reduce risk of preterm birth in a cohort of women who had a previous preterm delivery/ risk of preterm birth. Adequate maternal zinc intake is also critical for optimal brain development in infants and may have long-term consequences, the deficit impairing the process of learning and memory [147,148].

In the early neonatal period, adequate sources of zinc can be obtained from breast milk, but young children's poor nourishment is particularly affected. Zinc deficiency can affect microbiota composition [149] and impair immune function [150] contributing to the global burden of infectious diseases including diarrhea [145], pneumonia and malaria [151,152].

3.3. Deficiencies of Selenium

Selenium (Se) functions as an antioxidant and may play a crucial role in protecting the

fetus from the increased oxidative stress associated with pregnancy. A correlation between Se deficiency during pregnancy and the occurrence of obstetric and perinatal complications has been reported for recurrent miscarriage, preeclampsia, IUGR, preterm delivery and small-for-gestational-age birth weight [153]. Despite some evidence for positive effects of Se supplementation in pregnant women, further studies are required to confirm the benefits and safety of increased Se intake in this population group [154].

Moreover, Se may protect the developing fetal brain from oxidative injury. Se is also involved in thyroid metabolism, with importance for long-term neurodevelopment [155]. A low prenatal Se status has been negatively associated with infant psychomotor score at 6 months of life [156]. In contrast, a positive relationship has been observed between an adequate maternal Se status in pregnancy and cognitive and psychomotor abilities during toddlerhood and middle childhood [157].

Serum Se levels decrease in the first months of life, then show a progressive increase to reach constant values in children over one year of age [158]. Infants are born with Se reserves, but depend as they grow on the Se supplied by breast milk. Se levels in breast milk are high in colostrum, then decrease over lactation and are also strongly influenced by maternal Se status and diet. Furthermore, dietary intake of Se depends on the geographical region and the content of Se in the soil [159]. Nevertheless, overt Se deficiency is relatively rare in term infants. Keshan cardiomyopathy and Kashin-Beck osteoarthropathy are Se-deficient conditions of childhood identified only in certain areas where Se levels in the soil are extremely low [160].

3.4. Deficiencies of Iron

Iron (Fe) plays a key role in hemoglobin and myoglobin synthesis, oxygen transport, and the functioning of iron-dependent enzymes. Iron deficiency (ID) develops when the amount of stored iron is inadequate to meet body requirements and culminates in iron deficiency anemia (IDA) when stored iron is depleted and red cell production is impaired. The risk of ID or IDA is particularly high in pregnancy and infancy [161]. During gestation, iron needs increase compared to the pregestational period to cover maternal red blood cell expansion and the feto-placental growth [162]. After birth, the requirements for iron of the exclusively breastfed term infants are met primarily through the utilization of iron stores because the iron concentration in breast milk is low. At around 6 month of age, iron stores become depleted and introduction of iron-rich foods and even iron supplements is recommended for the rapid growth associated to infancy and toddlerhood [163].

IDA during pregnancy has been associated with preterm birth, small for gestational age, and low birth weight [164]. Although iron supplementation in pregnancy is still controversial in term of safety, an adapted supplemention to the maternal iron status may be recommended [165].

Furthermore, ID during pregnancy, infancy and early childhood may alter neurodevelopment processes such as myelination and neurotransmitter synthesis, resulting in cognitive and behavioral deficits that can persist throughout life, even after iron repletion [166]. Several studies reported long-term cognitive, motor, social-emotional and neurophysiologic abnormalities in both children and adults as a negative effect of ID early in life [167]. In addition, evidence from animal models suggests that maternal ID during pregnancy is associated with offspring obesity and hypertension later in life. However, such evidence is limited in human studies [168].

4. Deficiencies of n3 -, n6 - Polyunsaturated fatty acids (Carmen Ioana Mureșan)

Polyunsaturated fatty acids (PUFAs) can be classified among the omega-3 (n-3) or omega-6 (n-6) families. Some PUFAs cannot be synthesized de novo, and thus are essential fatty acids (EFAs) which need to be taken from the diet during pregnancy, fetal and neonatal period. The parent EFAs are linoleic (LA; 18:2, n-6) and α-linolenic (ALA; 18:3, n-3) acid, which can be further desaturated and elongated (by enzymes) into biologically active long-chain PUFAs (LCPUFAs). ALA can be converted into eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:6, n-3), and all three represent the most important and common PUFAs found in human milk [169]. DHA has a structural role in the brain grey matter and retinal membranes [170]. LA is metabolized in arachidonic acid (ARA; 20:4, n-6), which can be found in neural tissue [171], and is a precursor of compounds involved in immune response [172]. Still, due to genetic and environmental factors, the fetus and infant can have ineffective enzymes and cannot convert parent EFAs leading to deficiencies [173]. Also, a critical moment which can lead to deficiencies is during the last ten weeks of pregnancy -associated with important brain and nerve tissue development, when fetal demand for EFAs is high [174]. Still, these deficiencies can be surmounted by an adequate maternal diet during late pregnancy and in early neonatal life. Yet, in pathological conditions (i.e., intrauterine growth restriction, diabetes), maternal and fetal levels of LCPUFAs undergo significant changes and deficiencies can also occur [172]. Thus, in these conditions, more attention should be given to the mother's nutritional status. Another issue is the excess of various EFAs, which can diminish the bioavailability of others due to competitive desaturation leading to deficiencies and undesirable consequences such as slower neural transmission times and postnatal growth restriction [175, 176]. The benefits of EFAs supplementation were reported with controversial results. A recent meta-analysis [177] concluded that n-3 PUFAs do not improve visual acuity, growth or language development, whilst motor, cardiovascular health, behavior and immunity were affected.

Also, the Cochrane review [178] showed there is no significant effect of LCPUFAs supplementation. Still, n-3 LCPUFAs consumption could benefit preterm infant development [179-181] and the antiallergic effect in offspring is promising [182-184]. Although more

research is mandatory, the health organizations recognized LCPUFAs as key micronutrients in the first 1000 days of life [185]. The International European Food Safety Authority (EFSA) recommends 100–200 mg/day of DHA in addition to the adequate intake (AI) of 250 mg/day of EPA plus DHA during pregnancy and lactation. The EFSA panel proposes for DHA an AI of 50–100 mg/day for infants and 100 mg for the age of 6–24 months [186].

5. Impact of nutrition literacy of pregnant women and mothers on long-term health (Mădălina A. Coman, Bianca O. Duran, Ștefana A. Dobran)

Research in the field of nutrition and health determined that health and nutrition literacy levels of pregnant women directly affect their level of prenatal care and influence the outcomes of pregnancy. Breastfeeding, use of an emergency room, use of medication for infants, and feeding patterns for babies are all strongly influenced by the health and nutrition literacy of the mother [187,188]. Moreover, the nutrition of the mother determines both the physical and mental health of her child and unfavorable events can facilitate vulnerabilities and lead to several cardiovascular and metabolic diseases [189,190]. The body of research on pregnancy, lactation, infancy and early childhood has long established that nutrition has long-lasting effects on later health and disease for both communicable and non-communicable diseases. The phenomenon is referred to as "early metabolic programming of long-term health and disease "[191]. The most common diseases associated with poor nutrition during pregnancy, infancy and early life are cardiovascular diseases and neural tube defects (NTD's), which are characterized by severe defects of the brain and spine, clubfoot, diabetes, obesity and hypertension [192,193]. Nutrition requirements for pregnant women and mothers vary across countries, depending on the guidelines recommended and used. In order for these guidelines to be understood and followed, pregnant women and mothers need to have an adequate level of health literacy and nutrition literacy.

Health literacy is defined as “knowledge, motivation and competencies to access, understand, appraise, and apply health information in order to make judgments and make decisions in everyday life concerning healthcare, disease prevention and health promotion, to maintain or improve quality of life during the life course” [194]. Nutrition literacy is a form of health literacy that encompasses key elements from general health literacy and food literacy constructs [195].

Low levels of health literacy and nutrition literacy are associated with low levels of education and general literacy, and overall poorer health outcomes in individuals, pregnant women are not an exception [196]. Maternal diet during the pregnancy period is considered to be one of the influential factors on child health and development, affecting their long time health. Apart from that, it affects the health condition, both physical and psychological of women going through pregnancy and their early years of motherhood, as demonstrated in the

early chapters of this book. Nutrition education and counseling are strategies that are mostly used around the world in order to improve the health and nutrition literacy of pregnant women and mothers. Counseling about healthy eating and physical activity are extremely important in order to prevent excessive weight gain during pregnancies and in undernourished populations, education on increasing daily energy and protein intake is recommended [197].

World Health Organization (WHO) recommends using a context adapted strategy that is based on the following principles while suggesting further research and development of prenatal programs [198]:

1. Education about increasing the diversity and amount of foods consumed.
2. Education about adequate weight gain through sufficient and balanced protein and energy intake.
3. Education about consistent and continued use of micronutrients supplements, food supplements or fortified foods.

6. Conclusion

The quantity and quality of the micronutrients, vitamins and minerals, or PUFAs from food sources are critical for growth and development as well for biologic activity. The foetal and postnatal deficiencies caused by diet impairments could translate by health effects to infants and potential long-term effects (altering renal function, cardiovascular function, pancreas function, body composition, and pulmonary function). The nutrients needs are challenging for meeting their requirements with diet alone. In response, the recommended use of micronutrients supplements and fortified foods during pregnancy should be a mutual care pregnancy practice. Biotin (vitamin H or B7), vitamin D3, folic acid (vitamin B9), iron, iodine, zinc are extremely important for their potential to further improve infants outcomes beyond micronutrient supplementation. Although, micronutrient supplementation is an effective strategy during pregnancy, the in-depth studies are needed to translate into a public health policy recommendation by WHO, FDA (Food and Drug Administration) and EFSA (European Food and Safety Authority).

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