

## How Does Nutrition Influence Development?

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A growing fetus needs adequate nutrition in utero. Severely restricted maternal intake of calories or protein can cause decreased fertility, fetal death, premature delivery, and growth restriction. Deficiencies in some essential minerals or vitamins increase the risk of malformations and other adverse pregnancy outcomes.

Extreme caloric restriction leads to irregular menstrual periods or amenorrhea (lack of menstruation), both of which decrease fertility. During the last six months of World War II, a Nazi-occupied area of the Netherlands was completely cut off from food supplies in retaliation for a Dutch rail strike supporting the Allies. The average daily food ration decreased from 1400 calories to less than 600 calories (almost exclusively from bread and potatoes) during the last two months. Women who were pregnant or became pregnant during this famine suffered an excess of premature deliveries, very low-birth weight infants, and infant deaths. Similar poor outcomes were reported during the siege of Leningrad. The "fetal origins of adult disease" hypothesis purports that undernutrition during fetal life, infancy, and early childhood followed by nutritional plentitude resulting in a rapid increase in body mass index (a measure of weight for height) can increase the risk of chronic diseases including coronary heart disease, hypertension, and type 2 diabetes, underscoring the importance of good maternal nutrition during pregnancy.

Deficiencies in certain micronutrients cause congenital malformations in animals and humans. The relationship between a deficiency of iodine (needed for thyroid hormone synthesis), goiter, and cretinism, a neurologic disorder characterized by severe cognitive impairment, was identified during the nineteenth century and represents the earliest observation of the interconnection of diet and birth outcome. While iodine supplementation (primarily in the form of iodized salt) has eliminated goiter and cretinism in developed countries, more than 2 billion people (27% of the world population) still suffer from iodine deficiency disorders. Iodine deficiency during pregnancy also can cause fetal death, severe growth restriction, abnormal bone development, and varying degrees of mental impairment.

Vitamin A deficiency was first shown to be teratogenic in swine in the 1930s. Warkany and his colleagues extended these findings by detailing the defects that vitamin A deficiency produces in virtually every organ system of the rodent. More recently, vitamin A was shown to be critical in establishing anterior–posterior body axis patterns in the embryo. Sporadic reports in the literature have linked eye abnormalities and other adverse birth outcomes to severe maternal vitamin A deficiency. Malformations induced by vitamin A deficiency in humans are rare, but in developing countries, vitamin A deficiency remains the leading cause of visual impairment and blindness. Even though it is important to get enough vitamin A during pregnancy, too much vitamin A can also be teratogenic (discussed in the last paragraph of this chapter).

Deficiencies in many B vitamins adversely affect development. In animals, riboflavin, niacin, folic acid, and pantothenic acid deficiencies cause structural malformations; pyridoxine and thiamine

deficiencies increase embryonic mortality and decrease fetal growth. Folate deficiency, induced by a folic acid antagonist, causes structural malformations in animals. In humans, the neural tube defect rate among offspring of women taking folic acid supplements at the time of conception is reduced by as much as 50% compared to that among unsupplemented pregnancies. The U.S. Public Health Service recommends that all women receive 400 µg of folic acid daily, and since January, 1998, mandatory fortification of enriched cereal grain products with folic acid at a level designed to provide additional daily intake of 100 µg/day folic acid was fully implemented. Since fortification, there has been a 26% decrease in neural tube defects in the U.S. The Teratology Society resolution on folic acid fortification calls for mandatory fortification of a centrally produced food to provide at least an additional 150 µg folic acid per day in all countries to prevent folic acid-preventable spina bifida and anencephaly by 2024. It is controversial whether supplemental folate overcomes the effects of subclinical Vitamin B12 deficiency in the pregnant woman or a metabolic problem of the embryo. Low maternal Vitamin B12 status can lead to neurological developmental delay and megaloblastic anemia in the offspring and has been reported to be an independent risk factor for the occurrence of neural tube defects.

Using genomic sequencing, congenital vertebral and heart malformations in patients were shown to be caused by gene variants and loss of function in enzymes involved in the kynurenine pathway resulting in a reduction in de novo synthesis of nicotinamide adenine dinucleotide (NAD) from the essential amino acid tryptophan. When the CRISPR-Cas9 technology was used to produce the same pathogenic gene variants in mice similar congenital defects were observed. Niacin supplementation of the diet of these CRISPR-Cas9 mice during gestation increased NAD levels in the embryo and prevented the birth defects. This study shows that nutrient requirements are influenced by genetic variation (nutrigenomics).

Choline has recently been deemed an essential nutrient because the body cannot always produce enough to meet its need. Choline functions in the synthesis of membrane phospholipids and the neurotransmitter acetylcholine and participates in methylation reactions, including DNA methylation, which can affect gene expression via epigenetic mechanisms. In animals, low choline intake during late pregnancy alters brain structure and function whereas in utero choline supplementation can improve performance of cognitive or behavioral tests in the offspring. Long chain polyunsaturated fatty acids such as the docosahexaenoic acid (DHA) found in fatty fish have also garnered interest. Reports from animal and human studies suggest a possible relationship between DHA and visual acuity in the offspring.

Low maternal vitamin D status is associated with reduced infant growth, neonatal hypocalcemia, and poor bone mineralization. Vitamin D can be generated in the skin from 7-dehydrocholesterol upon UVB radiation and obtained from supplements and the diet (though vitamin D occurs naturally in relatively few foods). Dark skin, concealing clothing, sunscreen use, and northerly latitudes can limit sunlight exposure and reduce vitamin D synthesis. Recently, a high prevalence of maternal hypovitaminosis D and incidence of infants with rickets has emerged internationally, fueling the concern that vitamin D deficiency is an increasing public health problem. If a woman plans to exclusively breastfeed her baby, it is important that she has adequate vitamin D. The American Academy of Pediatrics recommends vitamin D supplementation (400 IU per day) for exclusively breastfed infants. In addition to the classical functions of vitamin D in calcium metabolism and bone health, there is increasing interest in delineating the extent to which vitamin D impacts the immune system as well as contributes to a number of diseases, including asthma, cancer, neuropsychiatric and cardiovascular disorders, and autoimmune diseases such as diabetes, multiple sclerosis, and rheumatoid arthritis.

Vitamin E deficiency in rats produced litters in which approximately 30% of pups had brain anomalies (exencephaly or hydrocephalus). However, there is no evidence that vitamin E deficiency

is teratogenic in humans. In contrast, vitamin K deficiency in humans (usually as a result of therapy with an oral anticoagulant, warfarin) results in a high percentage of miscarriages and prematurity. Infants have characteristic bone abnormalities, optic atrophy, and cognitive impairment.

Zinc deficiency is teratogenic in animals, affecting the development of virtually every organ system. After only 24 hours of dietary deficiency, plasma zinc decreases by 40%, and only a few days of deficiency during the embryonic period can produce malformations. Offspring of women with acrodermatitis enteropathica, a genetic disorder of zinc absorption, have a higher rate of malformations. Epidemiological studies also suggest a relationship between zinc deficiency and central nervous system malformations in humans. Although severe zinc deficiency is uncommon in developed countries, mild deficiency is common: the average dietary intake is only about half of the recommended daily allowance (RDA) for pregnant and lactating women. Also, some drugs, chemicals, and physiological or environmental stressors can significantly alter zinc metabolism. These two facts, along with the observation that even transitory zinc deficiency can have adverse effects, suggest that unrecognized, subclinical zinc deficiencies may play a role in some human embryonic morbidity.

The adverse effects of copper deficiency during pregnancy have been shown in numerous species, including humans. Copper-deficient lambs exhibit neonatal ataxia and myocardial atrophy. The effects of prenatal copper deficiency in humans have been reported in offspring with Menkes' disease, an X-linked disorder of copper metabolism. These infants have cognitive impairment and severe cardiovascular and connective tissue defects that generally cause death by three years of age. Many of the defects can be linked to decreased activity of copper-requiring enzymes. Copper-chelating drugs, including D-penicillamine, used to treat Wilson's disease (a genetic copper overload condition) and rheumatoid arthritis, can induce copper deficiency in humans.

Vitamins may be good for you, but more is not necessarily better. Megadoses of vitamins may be harmful in some instances. In animal models, an excess of vitamin A is teratogenic, affecting the development of many organs. Many genes responsible for establishing the embryonic body pattern are controlled by retinoic acid, the active form of vitamin A. Vitamin A levels are tightly controlled in the embryo to regulate expression of these genes. Excess vitamin A can overwhelm the control mechanisms, leading to abnormal development. It is likely that vitamin A excess would be teratogenic in humans, but it is not clear what the minimum teratogenic dosage is. The latest thinking is that this level is more than 30,000 International Units (IU)/day; the RDA for pregnancy is 2,670 IU/day). The Teratology Society, in a position paper on vitamin A issued in 1987, advocated that vitamin A intake in pregnant women be restricted to the RDA.

## Suggested Reading

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