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# The Role of Multimicronutrients on Improving Better Pregnancy Outcomes: A literature review

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## ABSTRACT

This paper describes the role of multimicronutrients on improving better pregnancy outcomes. Multimicronutrients are vitamins and minerals needed for normal body function, growth and development. There are 6 vitamins and minerals involved in heme synthesis, namely Cu, vitamin B2, folic acid, vitamin B12, Fe and vitamin B6 which are the main components in the formation of red blood cells and ensure the availability of oxygenation supply in the tissues. There are 6 vitamins and minerals involved in implantation and placentation, namely vitamin C, vitamin E, selenium, vitamin B1, vitamin B3 and vitamin D. There are 3 vitamins and minerals that work in overactivation of the regulatory growth pathways of the mother, Mammalian Target Of Rapamycin (mTOR) namely zinc, iodine and vitamin A which will stimulate placental expression and regulate GLUT-1 in the tissue that the affinity for glucose increases. There are 2 vitamins that play an important role in glucose metabolism and which can affect the availability of energy for the fetus, namely vitamin D and zinc. There are 3 vitamins and minerals that play a role in the synthesis of myelin and regulate the release of neurotransmitters for brain growth, namely folic acid, zinc and iodine, Fe, vitamin B6, vitamin B12 and vitamin C, and vitamin E. The administration of MMN also optimizes the collaboration network between antioxidants (antioxidant network), which occurs between all antioxidants through their respective mechanisms in counteracting free radicals. There is a synergistic relationship between vitamin C, E,  $\beta$ -carotene, selenium, and zinc as antioxidants.

**Keywords:** Role, multimicronutrient, pregnancy outcome

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## INTRODUCTION

Multimicronutrients are vitamins and minerals needed for normal body function, growth and development. Pregnant women need more vitamins and minerals than before pregnancy to support fetal growth and development, cell differentiation processes. micronutrients status play an important role in pregnancy and on improving better pregnancy outcomes. Following are the roles of some vitamins and minerals in pregnancy on improving better pregnancy outcomes:

### Vitamin B1 (Thiamine)

Vitamin B1 acts as a coenzyme for the decarboxylation of 2 keto acid (such as pyruvate) and transketolase (eg in the pentose phosphate pathway) Thymine pyrophosphate (TPP) is a coenzyme in the enzyme pyruvate dehydrogenase complex and ketoglutarate dehydrogenase, which catalyzes the oxidative carboxylation of pyruvate to acetyl changes COA. Thiamine diphosphate (TDP) is a coenzyme required in transketolase reactions, for example the direct oxidation pathways of glucose (pentose phosphate shunt) thereby increasing glucose utilization and modulate cognitive function.

### Vitamin B2 (Riboflavin)

Vitamin B2 plays a role in relation to several enzymes, especially heme which contains cytochrome and in Fe-S protein complexes in the process of food oxidation in producing energy in mitochondria (electron transport chain and oxidation of phosphorylation in cells. High vitamin B2 can mobilize iron from ferritin and its utilization for increase haemoglobin synthesis. Riboflavin

deficiency can cause metabolic disorders in other B vitamins, especially folate and vitamin B-6.

### Vitamin B3 (Niacin)

The active form of niacin is Nicotinamide Adenine Dinucleotide (NAD<sup>+</sup>) and Nicotinamide Adenine Dinucleotide Phosphate (NADP<sup>+</sup>) coenzyme in many oxidoreductase enzymes that are important in ATP production. Vitamin B3 triggers differentiation of lymphocytes (NK cells), cells that are found in the defense system of the human body to defend themselves from diseases and infections that help the process of implantation and placentation. Niacin is part of the enzyme NDA (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) from the enzyme dehydrogenase, which is needed as a catalyst for the hydrogen transfer reaction.

### Vitamin B12

Vitamin B12 acts as a coenzyme (cobamine enzyme: vitamin B12, niacin, riboflavin and manganese) for normal tissue growth, nerve cells and red blood cells (erythropoiesis). Erythroblast requires vitamin B12 and folic acid for proliferation during cell differentiation. Vitamin B12 acts as a coenzyme that provides a methyl group for DNA synthesis that affects nucleus formation in new erythrocytes. Vitamin B12 deficiency causes erythrocytes to mature and die early (erythroblast apoptosis). In addition vitamin B12 also as a cofactor of the enzyme methionine synthetase plays a role in the transfer of methyl groups in the methylation reaction changes in homocysteine to methionine (along with folic acid) which is important for the synthesis and metabolism of

neurotransmitters and phospholipids in the central nervous system. The state of vitamin B12 deficiency can cause hyperhomocysteinemia, which occurs when methylation of homocysteine to methionine is disrupted. Hucks et al. (2004). Elevated levels of plasma homocysteine cause endothelial damage (dysfunction) by regulating the O<sub>2</sub>-producing system that causes vasodilatation due to decreased availability of nitric oxide (NO), a vasodilator important for regulation of blood flow and known as a bioregulator molecule that mediates intracellular signals and intercellular in some physiological processes. In addition, folic acid is a major component in the formation of red blood cells, such as DNA production so that it is also needed for cell development and growth.

### Folic Acid

Folic acid plays a role in the metabolism of amino acids, as a cofactor in DNA synthesis and methylation reactions. Folic acid along with vitamin B<sub>12</sub> is needed for the synthesis of methionine synthase. Folic acid in the form of 5-methyltetrahydrofolate (5-methyl THF) functions as a methyl donor in the conversion of homocysteine to methionine, which causes changes in S-adenosylmethionine (SAM) a universal donor of methyl groups that play a role in DNA methylation and methylation of histone proteins that control the epigenetic process and gene expression. The condition of SAM deficiency will cause a decrease in cytosine methylation and cause chromosomal abnormalities.

DNA methylation is part of cell development and is inherited through cell division which acts as a determinant of changes in gene activity that is not caused by changes in DNA sequences (epigenetics), determinants of gene expression, maintaining DNA integrity and developing mutations. There are 3 mechanisms for epigenetic processes, namely DNA methylation, histone modification and non-RNA coding. The occurrence of epigenetic changes during pregnancy affects the methylation status of DNA in the brain which will cause changes in gene expression. Folate deficiency can cause a decrease in the cell's ability to carry out transmethylation reactions including DNA methylation, histone and RNA. Folic acid deficiency in pregnant women can lead to cognitive decline, behavioral changes and long-term brain changes that are irreversible.

Folate is a source of donations for methyl to thymine (DNA) groups that replace uracil. If folate is limited to uracil it will cause misincorporation into the DNA which is mutagenic, causing unstable and broken DNA (single strand break) (1).

### Vitamin B<sub>6</sub>

Vitamin B<sub>6</sub> is present in 3 forms, namely pyridoxine, pyridoxal and pyridoxamine. Vitamin B<sub>6</sub> acts in the form of pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP) as coenzymes in transamination, decarboxylation and other reactions related to metabolism of protein (amino acids). The other pyridoxine function is involved in the synthesis of niacin from tryptophan, in the production of acid precursors nucleic, in heme synthesis (for hemoglobin production). Vitamin B<sub>6</sub> plays a role in the synthesis of neurotransmitters so that the transmission of nerve cells in the brain becomes better.

### Fe (iron)

Fe (iron) plays an important role in forming hemoglobin and helps various metabolic processes of the body. Fe functions as a means of transporting oxygen from the lungs to tissues and electron transport equipment in energy metabolism. Metabolism, among others, as a catalyst in the conversion of beta carotene to vitamin A, as a reaction to purine synthesis (as an integral part of nucleic acids in RNA and DNA) and synthesis of carnitine to transport fatty acids; collagen synthesis and neurotransmitter synthesis. Fe plays a role in the process of removing lipids from the blood, producing antibodies, and detoxifying toxins in the liver.

Fe is needed as a cofactor of tryptophan hydroxylation enzyme which synthesizes serotonin and hydroxylation tyrosine which synthesizes neurotransmitters such as norepinephrine and dopamine so that they have a role in memory processing. Iron is also needed by oligodendrocytes for the process of myelination, especially neurons in the sensory (visual, auditory), learning and behavior systems. Iron deficiency can cause failure of mitochondrial function in producing energy for cell life (mitochondrial dysfunction) and damage to mitochondrial DNA structure (2). Damage and errors in mitochondrial signaling will interfere with some of the respiratory pathways or chains to become disconnected or obstructed resulting in increased nitrate oxidation, electron transport disturbances, and oxidative stress.

### Copper (Cuprum)

Copper (cuprum) is part of the copper binding protein (ceruloplasmin) which oxidizes Ferro ions (Fe<sup>2+</sup>) to Ferric ions (Fe<sup>3+</sup>) during the binding of iron to transferrin so that iron can be carried to tissues that need it. Copper prevents anemia, where copper as a component in ceruloplasmin acts to transport copper and oxidize ferro ions to ferric ions during the iron binding process with transferrin to help iron absorption. Copper also releases ferritin and liver deposits and stimulates the synthesis of heme or globin fractions. Copper acts as a component of respiratory enzymes (cytochrome oxidase) that play a role in the electron transport chain and increase energy release (ATP) in the placenta. Cuprum also acts as a component of superoxide dismutase, scavenges radical superoxide and prevents lipid peroxidation and cell membrane damage (3).

### Selenium

Micronutrient selenium which has strong antioxidant power produces prostacyclin (a substance produced by vascular endothelial cells) where prostacyclin will produce Leukemia Inhibitory Factors (LIF) a pleiotrophic cytokine secreted during the menstrual cycle and levels increase most during the implantation phase. There is evidence that LIF plays a role in implantation of blastocytes, ie provision of polyclonal antibodies to counteract the role of LIF proven to thwart implantation. Administration of LIF has been shown to cause implantation in vivo and in vitro studies and reduced LIF production is associated with abortion (Elnashar and Aboul, 2004).

Selenium, through selenoprotein (which contains selenocysteine) plays a role in the formation of an antioxidant internal glutathione peroxidase (GPx) antioxidant which is very important and widely found in the cytoplasm, which can reduce hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and lipid peroxide formed from the oxidation of fat in the body, thus inhibiting the increase of Reactive Oxygen

Species (ROS) / oxidative stress which plays an important role in the pathogenesis of preeclampsia which causes placental injury and hypoxic conditions. As an antioxidant, GPx helps maintain membrane integrity, protects prostacyclin production, and limits lipid oxidation, lipoproteins, and DNA damage.

Selenium prevents placental trophoblast cell oxidation. Selenium in the form of selenomethionine, regulates the activity of p53 protein, by increasing p53 DNA binding activity and stimulating DNA repair. P53 protein is often referred to as the guardian or protector of the genome. This protein prevents replication of damaged DNA in normal cells and encourages self-destruction of abnormal cells containing DNA. Selenium deficiency also affects the metabolism of thyroid hormone because selenium deficiency disrupts the production and function of the type I enzyme deiodinase which is a selenoprotein. This enzyme is important for the T4 deiodinase process in peripheral tissues.

### 1 Vitamin D

Vitamin D is a steroid prohormone, which plays an important role in calcium absorption by regulating calcium absorption in the small intestine and is associated with an adequate immune response during pregnancy (4). Vitamin D stimulates the synthesis of calcium binding proteins and phospholipids binding proteins in the small intestinal mucosa. Bone mineralization is positively associated with bone mineral density (BMD). Vitamin D deficiency causes a decrease in calcium absorption which causes the release of calcium from the bone to maintain circulating calcium concentration. Vitamin D also plays a role in stimulating the differentiation and proliferation of chondrocytes so that the growth of the bone growth plate is better, resulting in more body length addition compared to the iron supplementation group. The more nutrient content, the better absorption of vitamins so that its utilization is more effective for bone growth.

There are a number of biological pathways that explain the role of vitamin D that can affect maternal health, placental and fetal growth during pregnancy. In vitro research shows that vitamin D plays an important role in the metabolism of glucose and insulin which can affect the availability of energy to the fetus. Several meta-analysis studies, explaining the effect of vitamin D on reducing the risk of preeclampsia (4). During pregnancy there is a change and physiological adaptation in the mother's body, including changes in the immune response. Vitamin D modulates the immune system that can help shape the right maternal immune response to the placenta which also regulates the key target genes associated with proper placental implantation. Vitamin D plays a direct role in the production of antimicrobial peptides such as cathelicidin, which are produced after activation regulated by vitamin D receptors where production requires 25 (OH) D which plays an important role in preventing infection during pregnancy. Vitamin D also affects bone and muscle growth (1).

Recent research states that there is a direct role of vitamin D in the regulation of Hoxa-10 in human endometrial stromal cells which plays an important role in controlling uterine reception, implantation, and desidualization and will further influence the increase in fetoplacental blood flow. Vitamin D plays a role in the synthesis and release of human placental lactogen (hPL) by trophoblast cells. hPL through stat-5 or SOCS signal and mTOR1 increase mediated by S6K1 signal which induces insulin resistance will increase glucose gradient to the fetus. The active

hormone vitamin D, 1 $\alpha$ , 25 dihydroxyvitamin D3 (1,25 (OH) 2D3) increases the expression of DNA repair / damaged DNA repair mechanism.

### Zinc

Zinc plays a role in anemia status, in the formation of the porphyrin Hb ring, a aminolevulinatase (ALA) dehydratase becomes porphobilinogen (porphyrin precursor). Zinc plays a role in regulating cell growth through

- parts of zinc finger proteins (ZNFs), a group of proteins that function at a broad cellular and molecular level, play a role in cell division and proliferation of cells and tissues and directly regulate DNA and RNA synthesis. Zinc deficiency is associated with decreased DNA synthesis in the form of accumulation and maintenance of proteins which mediate the entry of the cell cycle into the S phase (Matteo Cassandri, 2017). Zinc deficiency increases oxidative stress, which causes DNA damage and can interfere with DNA repair responses.
- role in regulating growth hormone and IGF-1 for cell division (5)
- an important part of the antioxidant structure through the Cu / Zn SOD enzyme that works to protect fat cells from peroxidation (6)
- plays a role in IGF-1 (somatomedin) modulation, a hormone that has the same molecular structure as insulin which stimulates amino acids and glucose uptake.

Zinc as an integral part of enzymes (metaloenzymes) catalyzes enzyme reactions that depend on zinc (zinc dependent enzymes) such as carbonic anhydrase, carboxypeptidase, alkaline phosphatase and alcohol dehydrogenase, DNA and RNA polymerase which are important for protein synthesis, cell division, hormone metabolism, carbohydrate metabolism and protein and neurotransmitter metabolism (7). Zinc deficiency can cause a DNA repair mechanism that occurs in certain phases of the cell cycle, decreases programmed cell death (apoptosis) which has a very important role in embryogenesis and decreases cell proliferation causing oxidized DNA.

### Iodine

Iodine is needed to form the thyroxine hormone needed by the body to regulate growth and development from the fetus to adulthood (8). Through thyroid hormone, iodine plays a role in cell energy metabolism. Retinoic acid (RA) and thyroid hormones are very important for differentiation and organogenesis in embryos. The transport of thyroid hormones through the plasma cell membrane is facilitated by several classes of transporter proteins, one of which is monocarboxylate transporter-8 (Mct8), which is expressed mainly in the brain and placenta. Iodine deficiency increases H<sub>2</sub>O<sub>2</sub> and increases the reactive oxygen species (ROS) which can damage DNA and cause mutations.

### 5 Vitamin A

During early embryonic development, the main active form of retinoids is trans retinoic acid (atRA) a regulator of gene transcription, which regulates the formation of seed layers, spinal cord formation, neurogenesis, cardiogenesis, and development of the dorsal and ventral parts of the pancreas, lungs, kidney and eyes (9). Vitamin A also plays an important role for the development of the visual system (retina), inner ear, spinal cord, craniofacial area, thymus, thyroid gland, parathyroid, lungs and

urogenital system. ATRA also has the ability to induce nerve differentiation in early embryonic development. Signal retinoic acid plays an important role during gastrulation, which is in the regionalization of all three germinal layers along the anteroposterior axis (9).

#### Vitamin C (ascorbic acid, ascorbate)

Vitamin C is an essential ingredient needed by the body to form supporting tissues (connective tissue), absorption of iron from food, and play a role in iron metabolism. Vitamin C functions as a reducing equivalent donor in a number of certain important reactions and is concentrated in nerve endings, and is concentrated in high amounts in the brain, liver and skeletal muscles. Vitamin C plays a role in the process of angiogenesis, which will induce the formation of new blood vessels and cause an increase in A.spiralis remodeling which will affect the process of implantation and placentation. Vitamin C works together with vitamin E in inhibiting the oxidation reaction. Vitamin C binds to radical vitamin E which is formed in the process of breaking the reaction of free radicals by vitamin E, into free vitamin E which re-functions as an antioxidant (10,11). Vitamin C deficiency can cause the formation of hydroxyl radicals through the Fenton reaction which causes oxidized DNA.

#### Vitamin E

Vitamin E is a scavenger of free radicals (including peroxide). The main function of vitamin E is as an antioxidant by giving hydrogen from hydroxyl (OH) groups to the ring structure to free radicals. Vitamin E is in the phospholipid layer of the cell membrane and acts to protect fatty acids polyunsaturated and other cell membrane components of oxidation by free radicals, including the brain nerve cell membrane. The main cell membrane consists of polyunsaturated fatty acids which are very easily oxidized by free radicals. This lipid peroxidation process can cause damage to the structure and function of cell membranes. Vitamin E increases prostacyclin release, arachadonic acid metabolites that inhibit platelet aggregation, reduce uterine contractility, and increase vasodilation. Therefore, circulating tocopherols concentration is associated with fetal growth which will lead to increased blood flow and substance intake nutrition to the fetus (12). Vitamin E destroys free radicals to block the chain of initiation and destroy the propagation chain.

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