

Review Article

Micronutrient Formulations for Prevention of Complications of Pregnancy: An Overview

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Abstract

According to a relatively recent UNICEF report, 15% of the infant population of the world is of low birth weight with India accounting for one third of all the world's low-weight newborns. Twenty percent of all low birth weight infants die within a month. This mortality figure is higher in developing countries due to inadequate nutritional intake by pregnant women. Development of a new package of nutrient-rich food based on egg or milk or soybean proteins, containing multiple micronutrient supplements, available at affordable cost, may protect against morbidity and mortality among pregnant women as well as low birth weight in newborns. These benefits may continue to decrease morbidity and mortality during infancy and childhood and might reduce risk of chronic diseases in later adult life.

Key words: Eclampsia, epigenetic inheritance, low-birth weight infants, micronutrient supplementation, ovulipids, pregnancy

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INTRODUCTION

According to the UNICEF-2013 report entitled 'Improving Child Nutrition'¹, the achievable imperative for global progress, over 20 million children, including 15% of infants, were observed to be born with low birth weight throughout the world in the 2011, assessment year with India representing one third of the world's low birth weight population. Every year more than 20 million infants world-wide are born weighing less than 2500 g^{2,3}. World Health Organization (WHO) has defined low birth weight as the weight at birth being less than 2,500 g or 5.5 pounds⁴. This standard cut-off of low birth weight for global comparison is based on observations and reflects that low birth infants are 20 times more susceptible to death as compared to heavier babies of same age⁵. High mortality is commonly found in developing nations, when compared with developed ones. An underweight birth leads to poor health outcome and the individual is more prone to being infected by various diseases in later stages of life. Adequate nutrition supply during pregnancy is very essential for both child and maternal health. Pregnant women are vulnerable to inadequate nutritional status, because of the high nutrient demands during pregnancy⁶. Deficiency of micronutrients such as iron, folate, zinc and various vitamins such as A, B6, B12, C, E and riboflavin is very common in people of developing nations and highly represented in pregnant women⁷. Micronutrient deficiency is due to inadequate intake of nutritional food such as meat, fruits and vegetables and in some cases it is pertinent to note that infections may also lead to nutritional deficiency. Multiple micronutrient supplementations to pregnant women have been observed to be very helpful in preventing adverse outcomes of pregnancy by fulfilling the maternal demand, also improving immune status of child and mother⁸⁻¹⁶. The

WHO strongly recommends food supplementation of folic acid and iron to minimize the risk of iron deficiency anemia among pregnant women. These recommendations are being implemented by some developing countries. In a 'Step ahead' programme, supplementation of micronutrients can be provided at very nominal cost^{12,13}.

Certain studies accomplished in the last few decades indicate that multiple micronutrient deficiency is becoming a public health issue in developing nations due to its association with various metabolic disorders such as cardiovascular diseases (CVDs) and type 2 diabetes in later adult life^{6,7,14}. Maternal under-nutrition and micronutrient deficiency have also been demonstrated to be an important underlying cause of complications of pregnancy and low birth weight in neonatal and infancy^{9,12,13,15,16}. WHO and UNICEF have suggested that under-deficiencies of nutrition and maternal micronutrients are likely to be responsible for major complications in pregnancy and morbidity and mortality in the fetus^{13,17}. Micronutrient supplements during pregnancy can act as a precautionary measure for reducing the morbidity and mortality in infants as well as in treating maternal complications during pregnancy. Hence, supplement recommendations by UNICEF/WHO/UNU (United Nations University) for pregnant women are to include 15 micronutrients as follows: 400 µg folic acid, 30 mg iron, 800 µg vitamin A, 200 IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 microgram vitamin B12, 15 mg zinc, 2 mg copper, 65 micrograms of selenium and 150 µg of iodine, to be administered during the antenatal period. The comparative needs of micronutrients in three different conditions, viz., non-pregnant, pregnant and lactating women are shown in Table 1. The expert group of the International College of Nutrition proposed that this regimen needs further

Table 1: Essential micronutrients required in nonpregnant, pregnant and lactating women according to the recommendations of UNICEF/WHO/UNU⁵⁴

Micronutrients	Non-pregnant women	Pregnancy	Lactation
Iron (mg)	15	30	15
Zinc (mg)	8	11	12
Calcium (mg)	1000	1000	1000
Iodine (µg)	150	220	290
Selenium (µg)	55	60	70
Vitamin A (µg)	700	770	1300
Vitamin B (mg)	1.1	1.4	1.4
-Thiamin (B1) (mg)	1.1	1.4	1.6
-Riboflavin (B2) (mg)	14	18	17
-Niacin (mg)	1.2-1.5	1.9	2.0
-Vitamin B6 (mg)	2.4	2.6	2.8
-Vitamin B12 (µg)	0.4	0.6	0.5
Folate (mg)	75	85	120
Vitamin D (g)	5	5	5
Vitamin E (mg)	15	15	19

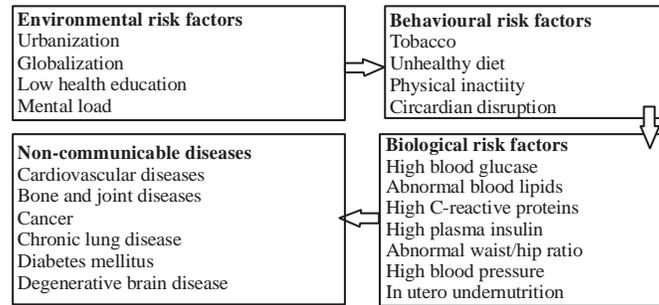


Fig. 1: Paths for non-communicable diseases

modification by adding chromium to prevent diabetes as well as omega-3 fatty acids, flavones and amino acids to enhance brain development and immunity among infants so as to prevent eclampsia, stroke, postpartum psychosis, hypertension, diabetes, dementia and depression in women in the next few months of follow up^{18,19}. These strategies can protect against nutritional problems related to under-nutrition and chronic diseases, cardiovascular diseases, diabetes, cancer, obesity, osteoporosis, chronic lung diseases and neurodegenerative diseases that occur in later life (Fig. 1).

MECHANISMS OF MICRONUTRIENT DEFICIENCY IN PREGNANCY

Since micronutrient deficiency is highly prevalent in the general population, it may worsen concurrently among pregnant women due to increased demand, because of oxidative stress and complications¹⁴. Micronutrients such as folate, iron, zinc, copper, selenium, iodine and vitamins²⁰ namely A, B6, B12, C, E and riboflavin are highly desirable during pregnancy due to their increased demand to serve the needs of fetus and mother^{6,7,14}. Iron is required for normal functioning of a large number of biological processes. Naturally, in pregnancy, the mother depletes her iron stores, one of the most essential micronutrients in order to fulfill demands of baby by an adequate amount. The transfer of iron from mother to fetus takes place through a complex mechanism. In the process of trans-placental transfer of iron²¹, the first step involves binding of transferrin (Tf)-bound iron to the transferrin receptor. Thereafter, the uptake of this iron bound complex is by an endosome, followed by acidification and then release of iron by a divalent metal transporter 1. The efflux of iron across the basolateral membrane is carried out through ferroportin and oxidation of Fe (II) by zyklopen²². Iodine, an essential micronutrient, works as a key component of the thyroid hormone metabolic processes, which are critically associated with fetal growth, development and

metabolism. There are various consequences of iodine deficiency, resulting in inadequate thyroid hormone formation. This deficiency can affect individuals of any age, gender and physiological conditions. Iodine deficiency during pregnancy may show an effect on fetal development, leading to mild intellectual blunting and to cretinism in children. Endemic cretinism, said to be the most serious iodine deficiency disorder is represented by symptoms of permanently stunted physical and mental development, caused by an untreated congenital deficiency of thyroid hormones as a consequence of severe maternal iodine deficiency²³. There is some information about deficiency of antioxidant flavonoids, omega-3 fatty acids and amino acids influencing immunity, neuronal function and cardiovascular risk as well as epigenetic inheritance of Non-Communicable Diseases (NCDs), which may also influence outcome of pregnancy^{4,8,13,14}. In respect of vitamin C, a study was accomplished indicating vitamin C deficiency during pregnancy was found to be positively correlated with development of 'Ever wheeze' and eczema during the children's second year²⁴. The greater need for certain nutrients during pregnancy may be because of red blood cell mass being expanded during pregnancy. This RBC mass is proportionally less than that of plasma, hence some biochemical levels for minerals and trace elements fall in plasma, for example, hemoglobin fall is parallel to red blood cell volume^{8,14}. Zinc and magnesium are also important during pregnancy but their concentration fluctuates at various stages of same. The zinc concentration declines progressively with pregnancy, whereas magnesium shows no gestational dependence, until late pregnancy, where, it declines continuously. The essentiality of zinc as a micronutrient is highly desirable in pregnancy because many fundamental processes are dependent on Zn. In addition to adequate intake during pregnancy and lactation, Zn is studied in number of researches that have a wide range of pathological outcomes which are associated with deficiency of zinc

including birth defects, impaired immune function and growth retardation, increased susceptibility to infection, skin disorders and central nervous system dysfunction²⁵. The selenium element is incorporated into various proteins to make selenoproteins, including the antioxidant enzyme, selenoprotein-P, glutathione peroxidase and thioredoxin reductases. Also, selenium is essential for thyroid hormones formation and thus for normal functioning of the thyroid gland. Overall maternal selenium concentrations and glutathione peroxidase activity decline during pregnancy^{25,26}. Copper plays a significant role in the human body. It is mainly involved in the formation of a wide range of enzymes and catalyzes various metabolic processes in mother during pregnancy and the developing fetus. During pregnancy, many changes may occur in copper levels due to transport in both mother and fetus. The serum copper increases in early pregnancy and continues to rise to reaching levels at full term approximately twice those found in non-pregnant women²⁵. Copper concentration increases in pregnancy but phosphorus remains constant, because of maternal adaptation. The primary bone-forming minerals calcium, phosphorus, magnesium and zinc are also contributing essential micronutrients. At the time of birth, an infant contains approximately 20-30 g calcium, 16 g phosphorus, 750 mg magnesium and 50 mg zinc, of which approximately 98, 80, 60 and 30%, respectively, are found in the skeleton of fetus²⁷. Calcium absorption increases initially in pregnancy, while the gradual decline is observed in protein-bound fraction in serum throughout the pregnancy, though the free ionic concentration remains relatively constant. The homeostatic control of ionic calcium is maintained by a complex interaction of vitamin D, parathyroid hormone and calcitonin. Enormous oxidative stress during pregnancy and eclampsia requires considerable doses of antioxidants to neutralize the free radicals, which may be damaging to both fetus and mother^{8,14}.

CAN MICRONUTRIENT MODULATE EPIGENETIC MECHANISMS?

It is possible that multiple micronutrient supplementations have a beneficial effect on molecular epigenetic markers of diseases in newborn, infants and on adult diseases that develop later in life^{19, 28-30}. Methylation of DNA, RNA and chromatids are common biochemical epigenetic mechanisms, which occur at regions of certain genes^{19, 28-31}. Nutrient deficiencies or excesses, pollutants and radiation can predispose cellular stress leading to DNA methylation. Cellular stress during replication induces many

minor deletions and duplications in the genome, adding fuel for human diversity and disease²⁸⁻³¹. Replication stress is known to be hazardous for the cell and is thought to contribute to ageing and cancer. DNA methylation is crucial for cell development and for stabilizing cell function, though the extent of methylation may be a determinant of dysfunction. There are multiple factors involved in epigenetic mechanisms, viz., specific nutrients and nutrient deficiency, exposure to other environmental factors, tobacco, western diet, pollutants and inherited genetic polymorphisms that can alter DNA methylation. The yellow Agouti mouse with obesity and yellow coat color variation is the best example of epigenetic inheritance due to nutrient deficiency in pregnant mice caused by hypomethylation of the Agouti gene³¹. This finding poses the possibility that nutrient supplementation to pregnant women might substitute the methyl group to repair the abnormal methylation of the Agouti gene and help in the prevention of obesity and metabolic syndrome^{32, 33}. Removal of the methyl group from normally methylated Agouti gene by increased supplementation of certain nutrients, namely, choline, betaine, folic acid and vitamin B12 may be helpful in repairing the deficit leading to normal methylation of genes, resulting in decreased risk of obesity and diabetes^{32, 33}. In one experimental study, Waterland and Jirtle altered the nutrient intake to serve as methyl group donors in mouse mothers, to cause methylation or demethylation of the Agouti gene by epigenetic modification³². In this developing mouse fetus, if the above modification occurs shortly after fertilization, the baby mouse may exhibit the yellow fur and obese phenotype with greater risk of developing cancer and diabetes¹⁷. However, the genetic code remains unchanged from normal mice. These nutrients; choline, betaine, folic acid and vitamin B12, in the diet of pregnant yellow Agouti mice may reduce the deleterious phenotypes in offspring, by donating methyl groups and allowing for the remethylation of the Agouti gene. If these mice be born with the Agouti phenotype, they can pass that deleterious epigenetic trait to their offspring, regardless of their diet during pregnancy. This landmark study indicates that nutrients can cause phenotypic changes, which can pass on through cell division and mating to the offspring due to their possible influence on natural selection³². There is a need to examine the effects of low omega-6: omega-3 ratio diet, flavones, arginine, taurine, cysteine, coenzyme-Q10 on remethylation of the Agouti gene and their effects on phenotypic variations. Any of these nutrients or nutraceuticals can provide the methyl group, which is added to DNA via folate and methionine pathways. The packaging and function

of the human genome are controlled by epigenetic mechanisms. However, it is not yet clear which methyl mark accounts for ageing or the development of diseases and how a nutrient deficiency or pollutant causes DNA damage. It is possible that the epigenome of a mother may be altered due to hormonal changes during pregnancy, which may interact with nutrients or nutraceuticals, mental stress, tobacco and or alcohol consumption and environmental pollutants resulting in expression of disease phenotypes^{32,33}. The mechanisms may involve proteins that interpret cytosine methylation signals and thus epigenetic changes may precede genetic changes in the arterial and vascular cells due to different biochemical factors, such as glycemia, hyperinsulinemia and pro-inflammatory cytokines, which may be responsible for development of chronic diseases in adult life. The DNA hypomethylation activates the relevant genes, for example, oncogenes in cancer and initiates chromosomal instability. However, DNA hypermethylation may also initiate silencing of protective genes resulting in cancers. These methylation patterns can develop molecular epigenetic markers for a variety of cancers, CVD and diabetes. The DNA sequence of humans appears to be under a strong influence of the genome and packed chromatin, which facilitates the differential expression of genes. Trans-generational response to nutrition, early life circumstances, development of adult diseases and longevity²⁸ as well as mechanisms of trans-generational epigenetic inheritance and their implications for the study of heredity and evolution, are underway^{33,34}.

EFFECTS OF MICRONUTRIENT ON COMPLICATIONS OF PREGNANCY

There is evidence that the repair of micronutrient deficiency among pregnant women immediately after 8 weeks of conception can reduce the prevalence of low birth weight babies and morbidity and mortality of mothers, new born and infants³⁵⁻⁴². In the case of low birth weight, supplementation of calcium, vitamin A, D and β carotene has been found to be protective against risk of subsequent type 2 diabetes, hypertension, heart disease, schizophrenia and depression in later life³⁵⁻⁴². The Tromso heart study proposed that poor nutrition during childhood and the Bogalusa heart study revealed that obesity during infancy could be one of the risk factors for adult cardiovascular diseases^{43,44}. It has been proposed that human adaptations occur in epigenetics, early in life, which may be before conception, to conserve nutrients and energy during deficient supply that becomes a risk factor

for adequate food supply⁴⁵⁻⁴⁸. In 1996, one author (first), while discussing with the late Dr David Barker and Dr Caroline Fall, proposed that deficiency of magnesium, zinc, chromium and omega-3 fatty acids during pregnancy appear to be important in the pathogenesis of CVDs and type 2 diabetes among offspring in later adult life. Caroline Fall is an international expert on micronutrient supplements among pregnant women^{49,50} and David Barker was an eminent epidemiologist in health and nutrition at Southampton University. Several expert groups on knowledge synthesis about determinants of low birth weight and preterm births and stillbirth, reported that micronutrient supplementation during antenatal period can prevent complications of pregnancy among mothers, morbidity and mortality among newborn and infants and risk of chronic diseases in later adult life^{16,47-52}. Of all these studies, in a recent randomized trial, women were provided supplements containing 15 micronutrients or iron-folic acid alone, taken daily from early pregnancy to 12 weeks postpartum, during a follow-up of 180 days⁵¹. These findings revealed that among the 22,405 pregnant women in the multiple micronutrient group and the 22,162% women in the iron-folic acid group there were 14,374 and 14,142 live-born infants, respectively. There were 764 deaths (54.0. per 1000 live births) in the iron-folic acid group and 741 deaths (51.6. per 1000 live births) in the multiple micronutrient group Relative Risk (RR), 0.95; 95% CI, 0.86-1.06). Multiple micronutrient supplementation resulted in a non-statistically significant reduction in stillbirths (43.1 vs. 48.2 per 1000 births; RR, 0.89; 95% CI, 0.81-0.99; P less than 0.02) and significant reductions in preterm births (18.6 vs. 21.8 per 100 live births; RR, 0.85; 95% CI, 0.80-0.91; P less than 0.001) and low birth weight (40.2 vs. 45.7 per 100 live births; RR, 0.88; 95% CI, 0.85-0.91; P less than 0.001). Despite no reduction in all-cause infant mortality up to age 6 months, this trial is a landmark⁵¹. Because of multiple micronutrient therapy, resulting in a non-statistically significant reduction in stillbirths and significant reductions in preterm births and low birth weight, these babies would be less susceptible to develop CVDs and type 2 diabetes in later adult life. Thus, antenatal multiple micronutrients compared with iron-folic acid supplementation is superior and further trials adding other micronutrients; magnesium, omega-3 fatty acids, amino acids can provide further benefits, particularly in vegetarian populations where people are rapidly adopting Western diet^{46,52}. In developed countries, antioxidant vitamin supplementations have not been reported to be protective⁴⁶. In a more recent clinical trial among 20 infants, ovulipids supplementation rich in amino acids and omega-3 fatty acids has been found to be protective

against metabolic syndrome⁵³. Folic acid or folate is a B vitamin, which is water soluble necessary for the healthy growth of the neural tube in the fetus which develops into the central nervous system constituted by brain and spinal cord. Without folic acid, the neural tube may not close correctly that may lead to spina bifida, a condition in which the spinal cord and or a sac filled with spinal fluid which protrudes through an opening at the back, or anencephaly. Folic acid supplementation can reduce the incidence of neural tube defects by 70%, according to the CDC (Centers for Disease Control and Prevention). The National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation funded study concluded that antenatal iron and folic acid supplementation should be encouraged in low- and middle-income countries and also at global level. Iron in addition to folate is one of the major trace elements required during pregnancy. Deficiency of iron in pregnancy can result in preterm delivery and maternal anemia. Adequate iron is required from conception, throughout the pregnancy and during lactation. Its deficiency during lactation may be associated with mental retardation^{10,14}.

DEVELOPMENT OF FOOD SUPPLEMENTS FOR PREGNANT WOMEN

In developing countries, major efforts are made to study the role of protein-energy malnutrition and deficiencies of micronutrients, mainly, iron, iodine and folic acid, because of diets being deficient in proteins-calories causing low-birth weight babies while, micronutrient deficiencies are related to anemia (iron, folic acid and vitamin B 12), hypothyroidism (iodine) and neural tube defects (folic acid)^{6,12,13,18,19}. However, it is now clearer that micronutrient appear to be responsible for overall health of the mothers and infants and hence, dietary supplements should be developed by the food industry for pregnant mothers, even men, planning to have children. Apart from 15 micronutrients proposed by WHO/UNICEF/UNU⁵⁴, which have been proven to be beneficial⁵¹, further new additions and dose increases of nutrients in the existing formulation appear to be a new strategy to achieve further benefit in morbidity and mortality of mothers and the newborn^{16,18,53}. It is possible that adding micronutrients to ovulipids can make it a super food for mothers as well as babies, for overall health and prevention of low birth weight. The infant milk formulation (Ovulipids IF) was based on guidelines of the ESPGHAN⁴ and contained 2.4 g P/100 cal (10%), 5.2 g F/100Cal (45%), 11.5 g C/100Cal (45%), based on duck egg, whey proteins and glucose syrups^{54,55}. This approach including egg as a base, along with

25 micronutrients may be a new package of nutrient rich super food for mothers as well as babies for health benefits. For vegetarians, milk or soy bean proteins along with 25 micronutrients could be an alternative approach. Both the approaches can provide super food supplements for prevention of morbidity and mortality among mothers and newborn and chronic diseases of these babies in later adult life.

WHO/UNICEF/UNU proposed 15 micronutrients; 30 mg iron, 400 µg folic acid, 800 µg RE vitamin A, 200IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 15 mg zinc, 2 mg copper, 65 µg selenium and 150 µg iodine, to be administered during the antenatal period. The Expert Group of the International College of Nutrition has proposed further modification by adding chromium and magnesium as well as omega-3 fatty acids, flavones, choline, betaine and amino acids, probiotics (approximately 25 nutrients) for further improvement in overall benefits^{32,56-62}. Choline, betaine, folic acid and vitamin B12 are known to prevent methylation of the DNA and chromatid, which is known to predispose metabolic syndrome in the offspring³²⁻³⁴. The quantity of some of the nutrients may also be enhanced for further benefits. Since cardiovascular diseases and type 1 and type 2 diabetes have emerged in epidemic proportions, this approach may be protective against these diseases⁶³.

CONCLUSION

In brief, multiple micronutrient supplementations during pregnancy appear to be protective against morbidity and mortality in mothers and low birth weight among newborn. These super food supplements may be developed for both vegetarians as well as non-vegetarians by using either egg, or milk with soybean and protein, along with 25 other micronutrients for health benefits. These benefits may decrease morbidity and mortality in the babies during infancy and childhood and thus possibly reducing the risk of chronic diseases in later adult life.

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