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Micronutrient Deficiency in Women Living in Industrialized Countries During the Reproductive Years: Is there a Basis for Supplementation with Multiple Micronutrients?

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Abstract

Maternal diet is widely recognized to be one of the major environmental factors influencing the development of the embryo and fetus. It is important that women of childbearing age maintain good nutrition throughout their reproductive years, including before conception, as there is a strong relationship between fertility and a successful pregnancy, and a sufficient intake of micronutrients. Yet even in 'high-income', industrialized countries, where dietary resources are more readily available, micronutrient levels in such women may be inadequate.

This review looked at the micronutrient status of women of childbearing age in industrialized countries, as well as those who were pregnant, to determine whether there are any gaps in micronutrient levels. A second objective was to assess whether the evidence indicates a role for multiple micronutrients other than folate and iron during these periods. Results indicated that although some women might have a sufficient intake of micronutrients (although not necessarily all of them), there are those who have lower than the currently-recommended daily intake of micronutrients, particularly folate, vitamin B12, vitamin D, calcium, iodine, iron and selenium. The evidence suggests that multiple micronutrient supplementation during the periconceptional period (i.e. before conception until the end of the first trimester) and throughout pregnancy could help to address inadequate dietary intake of micronutrients, improve maternal status prior to and during pregnancy, and thereby help to minimize reproductive risks.

Keywords: Maternal diet; Micronutrient deficiency; Multiple micronutrient supplementation; Periconceptional period; Reproductive health

Abbreviations: MMN: Multiple Micronutrients; MTHF: L-5-Methyl-Tetrahydrofolate; NTD: Neural Tube Defects; RBC: Red Blood Cell

Introduction

It is well established that good nutrition is important and that a balanced diet helps to maintain health in each of us. This is particularly true in women of childbearing age, as there is always the potential of becoming pregnant - and normal development of the embryo and fetus depends on the availability and supply of nutrients from the mother, and thus on her nutritional state [1-4]. In theory, women who are planning to have a child can accommodate the additional requirements through their diet, and a sufficient supply of micronutrients during the periconceptional period (i.e. the period before conception until the end of the first trimester) may support normal fertility, conception, placentation and embryogenesis and ultimately lead to better pregnancy outcomes [2]. However, the diet cannot always supply the micronutrients in the sufficient quantities required. In addition, not all pregnancies are planned; it has been estimated that up to 41% of pregnancies worldwide are unintended [5]. Thus, maintenance of optimal nutritional status throughout the reproductive years is essential.

Yet many women are at risk of insufficient micronutrient intake, and not just in developing countries [6,7]. This can be problematic, as deficiencies in micronutrients can affect fertility and can lead to adverse pregnancy outcomes such as neural tube defects (NTD), low birth weight, preterm deliveries, and pregnancy loss [1,2]. The health of the mother can also be affected by micronutrient deficiency, which contributes to anemia [8] and pre-eclampsia [1] for example. It is very important that women everywhere are made aware of the reality of suboptimal nutrition and the potential problems that can arise-and that inadequate intake prior to pregnancy usually cannot be rectified once pregnancy has been recognized [3]. Education as to the steps that can be taken to prevent micronutrient deficiency during periconception is vital. The simplest remedy is to consume a varied and healthy diet, which theoretically should be easy to do in more developed countries where women have greater access to good food. However, in reality, the micronutrient needs of many women are not always satisfied. In addition, it should be noted that deficiencies in vitamins and minerals can occur in both undernutrition and overnutrition [9].

Thus, micronutrient supplementation is necessary to address suboptimal nutrition before conception and during pregnancy. To date, periconceptional supplementation has focused on iron and folate, as much evidence supports the increased need for both during pregnancy [10]. There is a growing interest in supplementation with multiple micronutrients (MMN)-but is there a widespread need to supplement with other micronutrients, such as the B vitamins, calcium, vitamin D or iodine, for example? Is there any evidence to suggest that women of reproductive age in more developed countries have a suboptimal intake of such micronutrients? This review aims to offer a perspective of the micronutrient status of women of childbearing potential and pregnant women, to ascertain whether there any benefits associated

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with supplementation with micronutrients other than folate and iron before conception and during pregnancy.

Impact of insufficient micronutrients during periconception

The protective effect of folate during the first 28 days of pregnancy is a familiar and accepted concept, and supplementation is proven to significantly reduce the risk of congenital anomalies such as NTD [11-13]. When folate levels are inadequate, the risk of NTD increases [14,15]. Similarly, it has long been recognized that iron deficiency is the major cause of anemia in pregnancy worldwide [8], occurring in more than half of pregnant women in developing countries and almost one-fifth of women in developed countries [8,16]. Even women who enter pregnancy with reasonable iron stores can develop anemia in the later stages of pregnancy [4]. However, less is known about other micronutrients in periconception [1], such as the B vitamins, vitamin D, calcium, selenium and iodine. Table 1 provides a summary of the key adverse effects that are associated with an inadequate intake of these micronutrients during the periconceptional period.

What is increasingly being understood is that adequate nutrition has a role to play at all stages of periconception, not just during pregnancy [2,17]. Various nutrients may alter both maternal and fetal metabolism and thus influence pregnancy outcomes [1,2]. Inadequate nutrition before conception can negatively affect fertility and may have an adverse effect on implantation [2]. After conception, abnormal placentation is a risk if nutrition is poor [2], which can affect the supply of nutrients to the fetus throughout gestation [1]. Certain nutrients are involved in several biochemical pathways that ultimately affect cell replication and differentiation [18], and thus play a critical role in the development of the brain and nervous system during embryogenesis, while others influence oxidative pathways [1,2]. Abnormalities in placental function and oxidative pathways are associated with adverse effects such as pre-eclampsia, pre-term delivery, and fetal growth restriction [1,2]. Low folate and vitamin B12 levels increase the risk of NTD [2] as well as pregnancy loss [1]. The evidence supports the fact that there is a strong relationship between a sufficient micronutrient intake, good maternal health, and a successful pregnancy outcome [2].

Recommended micronutrient levels in females

It is clear that periconceptional nutrition is crucial for the successful onset and optimal development of pregnancy, delivery of a healthy child, and maternal health. However, the levels of micronutrients that are necessary during pregnancy are not always apparent. There are sometimes rather wide variations in the levels of micronutrients that are recommended by healthcare agencies and government bodies at different stages of life (Table 2) although there is

Micronutrient	Potential adverse effects of inadequate micronutrient intake	
	Effects on the offspring	Maternal effects
Vitamin A	Premature birth [74] Malformed offspring [2]	Vitamin A-deficiency anemia [2,74] Xerophthalmia [2] Night blindness [2]
Vitamin B6	Neurologic disease of infants [75] Impaired neuromotor development [3] Teratogenicity (omphalocele, exencephaly, cleft palate, micrognathia, digital defects, splenic hyperplasia) [3] Decreased body weight [3] Convulsions [3]	Pre-eclampsia [3,75] Anemia [2] Gestational carbohydrate intolerance [75] Hyperemesis gravidarum [75] Thrombosis [2]
Vitamin B12	Neural tube defects [3] Teratogenicity [3] Reduced fetal growth [75] Neurological abnormalities (cognitive disturbances, dementia, paresthesias, ataxia) [3,75] Fetal demyelination [3] Myelopathy	Anemia Megaloblastic anemia [75]
Folate	Congenital malformations (neural tube defects, orofacial clefts, cardiac anomalies) [3,75] Intrauterine growth retardation Premature birth [3]	Anemia [75] Megaloblastic anemia [3] Spontaneous abortions [75] Pre-eclampsia [75] Placental abruption [75] Thrombosis [75]
Vitamin D	Rickets [4] Impaired dental enamel formation [4] Reduced bone mineral accumulation	Osteomalacia [4,75]
Calcium	Intrauterine growth retardation [75] Low birth weight [75]	Pre-eclampsia [75]
Iron	Oxidative damage to fetal erythrocytes [75] Intrauterine growth retardation [75] Neonates small-for-gestational age/low birth weight [4,75] Premature delivery [4] Cognitive and behavioral problems [4]	Anemia [2,4] Increased corticotropin-releasing hormoneand cortisol production [75]
Zinc	Intrauterine growth retardation [4] Teratogenicity [75] Embryonic and fetal death [4] Small-for-gestational age infants [4] Preterm delivery [4]	Gestational hypertension [4] Pre-eclampsia [4] Intrapartum hemorrhage [4]
Iodine	Spontaneous abortions [4] Increased perinatal mortality [4] Mental retardation, cretinism [4]	Thyroid enlargement [4]
Selenium	Intrauterine growth retardation [75]	Recurrent abortions [75] Pre-eclampsia [75]

Table 1: Impact of inadequate micronutrient status during preconception or pregnancy.

a general consensus that micronutrient requirements increase during pregnancy. Furthermore, apart from folic acid the importance of other micronutrients is rarely disseminated to women planning a pregnancy, beyond the need for a 'varied and healthy' diet [17]. Even in the US, which offers a comprehensive preconception healthcare plan, the clinical need for a sufficient intake of micronutrients other than folic acid seems not to be overtly communicated directly to women [19]. This is something that should be addressed, and research should enable guidelines to become more consistent as preconception care begins to emerge and develop worldwide.

An adequate micronutrient intake is not always possible

In industrialized countries, it could be assumed that most women would have easy access to fresh and nutritious foods to maintain a healthy and balanced diet. However, the reality is that women in society are from a diverse range of social, economic, educational, ethnic and cultural backgrounds, all of which have an impact on what they consume. For example, women from low-income families might not always have the money to buy fresh foods, or the means to travel to places that sell them; instead, they may live in areas populated by convenience stores (that often stock only energy-dense but micronutrient-poor processed foods) and fast-food restaurants. Vegetarians and vegans are often lacking in certain essential micronutrients such as vitamin B12, which is primarily derived from animal products. Certain genetic disorders may prevent digestion or absorption of specific foods, leading to a deficiency in vital micronutrients; for example, lactose intolerance precludes consumption of dairy products, leading to low calcium intake and impaired vitamin D status [20]. An increasingly hectic and stressful lifestyle can result in poor eating habits such as skipping meals and increased consumption of fast foods. Weight loss is ever a concern to many women and the endeavor to reach the perfect weight may result in an adequate consumption of micronutrients. There are numerous factors that may adversely influence a woman's micronutrient status, some of which are listed in Table 3.

Micronutrient status of women in the general population

Despite the recommendations provided by healthcare and government bodies regarding the importance of consuming a varied and healthy diet in the periconceptional period, micronutrient intake can be inadequate in women of childbearing age [2] and in pregnant women [6]. For example, a high proportion of women of childbearing potential have been shown to have folate levels that are suboptimal (i.e. around 500-600 nmol/l, whereas that thought to be protective of NTD is 906 nmol/l) [21-23]. Similarly, mean iron intake in women aged 25-

Micronutrient	**WHO 2004** [10]	**IOM 2011** [76]	**D-A-CH 2000** [7,77] *	**Australia and NZ 2005** [78]	**UK Gov 2014** [79]	**Russia 2008** [80]	**China 2013** [81]	**Japan** [82]
Vitamin B2 (riboflavin), mg/d	14-18 y: 1.0 19-50 y: 1.1 Pregnancy: 1.4	14-18 y: 1.0 19-50 y: 1.1 Pregnancy: 1.4	19-24 y: 1.5 25-50 y: 1.4	14-50 y: 1.1 Pregnancy: 1.4	15-50 y: 1.1 Pregnancy: 1.4	1.8 Pregnancy (2nd half): 2.0	14-50 y: 1.2 Pregnancy: 1st trimester: 1.2 2nd trimester: 1.4 3rd trimester: 1.5	15-17 y: 1.4 18-49 y: 1.2 Pregnancy: 1.5-1.7†
Vitamin B6 (pyroxidine), mg/d	14-18 y: 1.2 19-50 y: 1.3 Pregnancy: 1.9	14-18 y: 1.2 19-50 y: 1.3 Pregnancy: 1.9	1.5	14-18 y: 1.2 19-50 y: 1.3 Pregnancy: 1.9	15-50 y: 1.2 Pregnancy: 1.2	2.0 Pregnancy (2nd half): 2.3	14-49 y: 1.4 Pregnancy: 2.2	15-17 y: 1.3 18-49 y: 1.2 Pregnancy: 1.4-1.5†
Vitamin B12 (cobalamin), µg/d	14-50 y: 2.4 Pregnancy: 2.6	14-50 y: 2.4 Pregnancy: 2.6	3	14-50 y: 2.4 Pregnancy: 2.6	15-50 y: 1.5 Pregnancy: 1.5	3.0 Pregnancy (2nd half): 3.5	14-50 y: 2.4 Pregnancy: 2.9	15-17 y: 2.5 18-49 y: 2.4 Pregnancy: 2.8-2.9†
Folate, µg/d	14-50 y: 400 Pregnancy: 600	14-50 y: 400 Pregnancy: 600	15-19 y: 300 [83] 20+ y: 400 Pregnancy: 550 [7]	14-50 y: 400 Pregnancy: 600	15-50 y: 200 Pregnancy: 300	400 Pregnancy (2nd half): 600	14-50 y: 400 Pregnancy: 600	15-17 y: 250 18-49 y: 240 Pregnancy: 480-490†
Vitamin D, µg/d	14-50 y: 5 Pregnancy: 5	14-50 y: 15 Pregnancy: 15	5	14-50 y: 5 Pregnancy: 5	Pregnancy: 10[84]	10 Pregnancy (2nd half): 12.5	14-50 y: 10 Pregnancy: 10	15-17 y: 6.0 18-49 y: 5.5 Pregnancy: 12.5-13.0†
Calcium, mg/d	14-18 y: 1,300 19-50 y: 1,000 Pregnancy, 3rd trimester: 1,200	14-18 y: 1,300 19-50 y: 1,000 Pregnancy: 14-18 y: 1,300 19-50 y: 1,000	1,000	14-18 y: 1,300 19-50 y: 1,000 Pregnancy: 14-18 y: 1,300 19-50 y: 1,000	15-18 y: 800 19-50 y: 700 Pregnancy: 700	1000 Pregnancy (2nd half): 1300	14-17 y: 1000 18-50 y: 800 Pregnancy: 1st trimester: 800 2/3 trimester: 1000	15-49 y: 650 Pregnancy: NS
Iron, mg/d	14-17 y: 19.6-65.4 18-50 y: 20.7-58.8 Pregnancy: 7.5-22.6	14-18 y: 15 19-50 y: 18 Pregnancy: 27	10	14-18 y: 15 19-50 y: 18 Pregnancy: 27	15-50 y: 14.8 Pregnancy: 14.8	18 Pregnancy (2nd half): 33	14-17 y: 18 18-49 y: 20 Pregnancy: 1st trimester: 20 2nd trimester: 24 3rd trimester: 29	15-49 y: 10.5‡ Pregnancy: Early stage: +2.5 Mid to late stage: +15.0
Iodine, µg/d	14-50 y: 150 Pregnancy: 200	14-50 y: 150 Pregnancy: 220	19-50 y: 200	14-50 y: 150 Pregnancy: 220	15-50 y: 140 [85] Pregnancy: 140 [85]	150 Pregnancy (2nd half): 220	14-50 y: 120 Pregnancy: 230	15-17 y: 140 18-49 y: 130 Pregnancy: 240-250†
Selenium, µg/d	14-50 y: 26 Pregnancy: 2nd trimester: 28 3rd trimester: 30	14-50 y: 55 Pregnancy: 60	30-70	14-50 y: 60 Pregnancy: 65	15-50 y: 60 [86] Pregnancy: 60 [86]	55 Pregnancy (2nd half): 65	14-50 y: 60 Pregnancy: 65	15-49 y: 25 Pregnancy: 30

*Values provided as listed in Elmadfa 2009, for non-pregnant women [7]; † depending on age; ‡ menstruating women. NS: Not Stated; RE: Retinol Equivalent

Table 2: Example recommended nutrient intakes of certain micronutrients in females.

Factors		Comments
Social and economic	Poverty/low income [87-89]	May limit access to nutritious foods [90], little dietary diversity [89] May have poor knowledge of nutrition [89] Associated with most of the major risk factors for adverse pregnancy outcomes [87]
	The need to work [87]	Inadequate time for shopping and food preparation [87] Work-related travel alters eating habits (e.g. missed meals) [87] Increased consumption of low-calorie (often nutritionally-poor) diets [87]
	Occupation [90]	Certain jobs are associated with low socioeconomic status (e.g. manual labor, driving), food choice may be limited or irregular [90]
Lifestyle	Alcohol consumption [87]	Excretion of high levels of zinc [87] Altered transport of amino acids across the placenta [87] Overall decrease in maternal nutritional status [87]
	Smoking [87]	Associated with poor eating habits (e.g. skipping breakfast) [87] May alter the metabolism of certain micronutrients [87] Can result in decreased antioxidant status [87]
	Illicit drug use [87]	Can lead to poor eating habits [87]
	Vegetarianism/veganism [91]	Can restrict intake of micronutrients mainly derived from animal products (e.g. vitamin B12) [91]
Health-related	Dieting [87]	May lead to substantially lower than recommended levels of calories, protein, vitamins and minerals [87]
	Health conditions/medication use [87]	For example, chronic digestive diseases can reduce micronutrient absorption, while HIV infection is associated with several nutritional deficiencies [87] Medication use may reduce absorption of micronutrients (e.g. oral contraceptive use is associated with reduced folic acid, B6 and B12 levels, and certain rheumatoid arthritis drugs are folic acid antagonists or interfere with iron absorption) [87]
	Genetic disorders	May prevent digestion or absorption of specific foods, leading to a deficiency in vital micronutrients (e.g. lactose intolerance reduces tolerance of dairy products, leading to low calcium intake and impaired vitamin D status [20]
	Micronutrient/food interactions	Certain foods or micronutrients can inhibit the absorption of other micronutrients; for example, zinc absorption is inhibited by phytate (in staple foods such as cereals, corn and rice), while increasing amounts of zinc in a meal can itself decrease the absorption of zinc [92]
Geographical	'Food deserts' [89]	People in some urban environments (e.g. low-income areas) and rural settings might need to travel to shops that sell more nutritious food, and instead may rely on local convenience stores (generally a poor selection of foods) [89,90] Those with a lack of mobility (e.g. lack of transport) may not have access to nutritious food sources [89]
	Home-grown or farmed produce [90]	Food choice is season dependent, which can limit choice [90] In some regions, the soil may lack certain micronutrients (e.g. selenium in China, [93] iodine deficiency in mountainous or flood-risk regions [94])

Table 3: Factors that may adversely affect the nutritional status of women.

49 years has been shown to be one-third lower than the recommended level [24]. Thus, we decided to explore more closely whether such women receive an adequate intake of the micronutrients required during each stage for a healthy pregnancy-whether that pregnancy was planned or not. In general, micronutrient status and deficiency have been assessed in pregnant women from developed countries [25]. But what about the micronutrient status of women in the general population of 'high-income' countries, without pre-existing medical conditions and who presumably have the resources to consume an adequate diet to meet their nutritional needs? Does their micronutrient status reach the recommended levels suggested in the guidelines? If not, how large is the gap? Is there any change in status from those of childbearing potential (including young girls) to those who are already pregnant? To this end, we searched the literature for studies published within the last 10 years that would provide evidence of the micronutrient status of women of childbearing age or those who were pregnant in the general population in high-income countries. Although different methods of data collection (e.g. 24 h dietary recalls, Food Frequency Questionnaires, blood samples) and different age classifications were used in the studies found, the data nevertheless provide an overview of the nutritional status.

In general, as outlined in Supplementary Table 1, it was found that for each micronutrient there are women who at least have an adequate daily intake (within the countries for which data is available)-and those who in fact have a surfeit. It is apparent that these women already consume a nutritionally-sufficient diet and/or may be using micronutrient supplementation (particularly during pregnancy) and/or live in a country where food fortification (with folate and/or iron) is mandatory. However, more often than not the nutrient intake or serum concentration of most micronutrients is inadequate, as outlined in the summary of Supplementary Table 1.

Folate: There was insufficient folate intake across all countries for which data was found, in all of the populations included and across all ages. Where folate was insufficient, intakes ranged from 23% to 98% of the recommended nutrient intake in non-pregnant women [7,26-28] (depending on the reference value used), and between 30% and 95% in pregnant women [7,29-37]. Intake was regularly less than half of the daily amount required [7,27,28,31,33,36,37]. The exception was in non-pregnant women in Japan [34], whose folate levels were apparently sufficient (Table 2); however, the recommended level of folate for such women in Japan is lower than for other countries, apart from the UK (Table 2). In the studies that looked at folate status during several stages of pregnancy, inadequate levels could be seen at each stage (between 33% and 78% of the recommended levels) [31-36].

Vitamin B2 (riboflavin): There was some evidence of inadequate intake in non-pregnant [7] and pregnant [7,29] younger women in European countries (where insufficient intakes were between 74% and 92% of the recommended daily intake) and in older pregnant women in Japan [34] (76% and 82% of the recommended intake in the first and second trimester, respectively); otherwise, there was an overconsumption of riboflavin in the women included [7,29,34,38].

Vitamin B6 (pyroxidine): On the whole, pyroxidine consumption was sufficient in non-pregnant women (younger and older) [7,38]. However, there was mild insufficiency in non-pregnant women in Japan [34] (73% of the recommended intake) and in some pregnant women in Austria [7], Canada [32] and Japan [34,35], where inadequate intakes between 65% to 95% of the recommended daily intake were observed.

Vitamin B12 (cobalamin): There was some deficiency in cobalamin intake in non-pregnant women (42% [7] and 55% [28] of the recommended intake in Europe), as well as in some pregnant women in Belgium [30], Spain [31] and Australia [33]. In both Spain [31] and Australia [33], intake decreased over the course of the pregnancy, while in Australia the intake increased again after giving birth [33]. There appears to be a surfeit of vitamin B12 in pregnant women in Japan [34,35], where vitamin B12 levels were double the recommended levels, as well as in non-pregnant adolescents girls in Europe [7], non-pregnant women in the USA [38], pregnant adolescent girls in the UK [29], and pregnant women in Canada [32].

Vitamin D: Insufficient vitamin D intake was widespread across all women, often to a large extent. In non-pregnant women, insufficient intake ranged between 22% to 88% of the recommended intake [7,38,39], and most intakes accounted for less than one-quarter of the daily amount required [38]. The situation was similar in pregnant women, where insufficient intakes ranged from 21% to 97% of the recommended amount [7,40-78]. However, intakes were more often closer to the recommended nutrient intake (e.g. >75% of the amount required). The greatest insufficiency was observed in China [44-46], Japan [47] and the USA [38,48], but was less apparent in Denmark [40], Sweden [39], New Zealand [42] and Australia [43]. Adolescent girls seemed to be at a high risk of vitamin D deficiency, whether pregnant (UK [29], Austria [7]) or not (Europe [7]). Vitamin D intake appeared to decrease slightly during the course of a pregnancy [40,41].

Calcium: Calcium intakes were insufficient in many cases, ranging from 50% to 82% of recommended levels in non-pregnant women [7,38] and 61% to 92% in pregnant women [7,29,49]. Non-pregnant younger girls appeared to be at greatest risk of inadequate intake in Europe [7].

Iron: Suboptimal levels of iron were evident in both non-pregnant [7,26,38] and pregnant women [7,29,50,51], according to the varied recommendations set by each country or region. In non-pregnant women, the intakes were particularly low across Europe [7,26], making up just 13% to 68% of the recommended levels with most inadequate intakes below 50%. Even in the US, where flour fortification with iron is mandatory [52], the intake was only three-quarters of the required amount [38]. In pregnant women, iron intake was slightly higher but was still insufficient in many cases [7,29,50,51].

Iodine: Inadequate iodine intake could be seen in all women, across all countries. Intakes that were insufficient ranged from 15% to 77% of the required amount in non-pregnant women [7,53,54], and were mostly at the higher end in pregnant women (ranging from 36% to 96%) [7,55-57].

Selenium: Selenium intake was mostly sufficient in non-pregnant women [7,38], although a slightly low intake was observed in Australia [26] (around 80% of the recommended intake). In pregnant women in the UK [58], selenium intake was generally adequate although some women had a lower than recommended intake.

Overall, these studies suggest that apart from riboflavin and possibly pyroxidine, there are inadequate nutrient intakes or blood concentrations of most micronutrients in women of childbearing potential, as well as those who are pregnant. In all of these women, a healthy, balanced diet rich in the micronutrients essential for a healthy pregnancy could ideally prevent such inadequacies. However, as already discussed nutritional intake is highly dependent on a woman's financial situation, social and cultural background, and personal habits [59], which often lead to poor dietary habits and a suboptimal diet. Even women who seemingly consume a sufficient amount of most micronutrients may have a suboptimal intake of one or two essential vitamins or minerals.

Role of supplementation

Based on the available evidence, it is clear that it is not only deficiencies in iron and folate that need to be addressed in women of childbearing potential in industrialized countries, but that there is also an inadequate intake or blood concentration of multiple micronutrients. Undoubtedly, there is a need for greater eduction regarding the importance of good nutrition in women of all ages, but particularly during pregnancy. It is vital that women of childbearing potential are fully aware of the importance of a good supply of fresh food, for their own wellbeing as well that of the developing child. Nevertheless, there is a rationale to supplement with multiple micronutrients before conception and during pregnancy, based on the adverse effects that an inadequate nutrient status can produce during this time, both in the developing embryo (e.g. the development of NTD and other congenital abnormalities, decreased birth weight, increased incidence of stillbirth) and in the mother (e.g. increased anemia and pre-eclampsia) [1,2]. Supplementation with multiple micronutrients could improve micronutrient status and thereby allow normal fertility, improve maternal health, and ultimately lead to the healthy development of a baby. However, is there any evidence that MMN supplementation before conception and during pregnancy will provide real clinical advantages?

From a pharmacokinetic standpoint, an MMN supplement that includes folic acid at a daily dose of 800 μg has been evaluated in healthy women of childbearing potential [21]. The study aimed to ascertain at what point red blood cell (RBC) folate levels considered preventive of NTD (906 nmol/l [14]) could be reached. In this study, it was observed that the RBC folate concentration, as a surrogate marker for NTD, increased to a protective level within 4 weeks in more than two-thirds of women, whereas at least 8-12 weeks of daily intake was required at a dose of 400 μg/day as observed in other studies [60-62]. In women who took longer than 4 weeks, a significantly lower baseline folate status compared to the other participants was observed. Furthermore, compared with placebo at 4 weeks and up to 16 weeks, MMN supplementation resulted in significantly higher levels of vitamins B12, B6 and B2, and a significantly lower concentration of homocysteine (where high levels are a risk factor for adverse pregnancy outcomes, including NTD [63]). These results were confirmed in a later study using an MMN supplement containing 400 μg folic acid plus 451 μg L-5-methyl-tetrahydrofolate (MTHF), which also determined its efficacy in achieving NTD-protective RBC folate levels [23]. It was observed that within 4 weeks compared with placebo, the MMN supplement was effective at replenishing RBC folate concentrations to a level considered to prevent NTD. In addition, there was a significant increase in the levels of folate and vitamin B6, while homocysteine concentrations significantly decreased.

Do these increases in RBC folate levels translate to a reduction in NTD and other congenital malformations? A randomized controlled trial using a similar MMN supplement (also containing 800 μg folic acid) in a Hungarian cohort determined that approximately 92% of NTD may be prevented using the MMN supplement, while the total prevalence of congenital abnormalities decreased by around

50% compared to no supplement [64]. Other studies have also demonstrated that MMN supplementation has beneficial effects on pregnancy outcomes. In an analysis of pooled outcomes from 16 high quality trials, there was a significant reduction in the incidence of low birth weight and small-for-gestational age (SGA) births with MMN supplementation, as well as an increase in mean birth weight [65]. This time there was an increased risk of neonatal death with MMN supplementation-but only in the subgroup of studies that began the intervention after the first trimester, again emphasizing the importance of the timing of initiation of MMN supplementation. A recent meta-analysis of MMN supplementation showed that the use of multivitamins rather than folic acid alone during the periconceptional period resulted in a modest but persistent reduction in limb reduction defects and congenital urinary tract abnormalities [66]. In addition, the risk of pre-eclampsia was reduced by 27%, multiple congenital abnormalities by 43%, and occurrent NTD in high-income countries by 49%.

In China, in a study of almost 61,000 women from socioeconomically disadvantaged areas, the incidence of stillbirth, malformation and low birth weight babies was significantly lower with MMN supplementation taken from at least 3 months before pregnancy compared with no nutrient interventions [67]. A meta-analysis of 17 randomized controlled trials in low- to middle-income countries indicated that SGA births were significantly reduced with MMN supplementation compared with standard iron-folate supplements [68]. Overall, there was no significant increase in the risk of neonatal mortality. It was observed that participants remained anemic in the included studies, despite seemingly inadequate amounts of supplemental iron; it was noted that starting the supplementation during pregnancy may be too late for many women, especially those with pre-existing anemia [68]. This highlights the fact that timing of initiation of MMN supplementation is an important aspect that should be considered; supplementation should begin before conception.

There is some concern that excessive periconceptional supplementation with folic acid may modulate DNA methylation, with potential epigenetic effects and long-term health consequences in the child [69-73]. Nevertheless, the number of studies is currently limited and the clinical significance of chronic or high folic acid intake is not well established [72,73]. There is a need for future studies to thoroughly investigate any potential adverse effects, but in the meantime the data is insufficient to impact on the proven benefits of folate supplementation [72,95-98].

Summary

The evidence suggests that a proportion of women in high-income countries-of childbearing potential or who are already pregnant-have lower either than currently-recommended nutrient intakes or blood concentrations of micronutrients, particularly folate, vitamin B12, vitamin D, calcium, iodine, iron and selenium. All of these women would benefit from supplementation with multiple micronutrients, rather than just folate and iron. Studies have confirmed that MMN supplementation can redress insufficient micronutrient levels and help to improve the health of both the developing embryo (e.g. by reducing the risk of NTD and other congenital abnormalities, increasing birth weight, and reducing the incidence of stillbirth) and that of the mother (e.g. by tackling anemia and pre-eclampsia). Timing of the intervention is critical, as supplementation during pregnancy is often too late to prevent adverse outcomes. To support the optimal reproductive health of women of childbearing potential and pregnant women from a nutritional perspective, MMN supplements should be taken at least one month before conception and throughout pregnancy.

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Author Contributions

ES was responsible for the concept of the review, fully reviewed the manuscript at every stage, and gave final approval.

Conflicts of Interest

The author is currently a full-time employee of Bayer Consumer Health.

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