Human Nutrition: Review Article

Annals of Nutrition & Metabolism

Ann Nutr Metab 2019;74:269–278
DOI: 10.1159/000499698

Received: October 8, 2018
Accepted: March 16, 2019
Published online: April 2, 2019

Impact of Micronutrient Status during Pregnancy on Early Nutrition Programming

Irene Cetin[a] Kai Bühling[b] Cansun Demir[c] Ashraf Kortam[d] Susan L. Prescott[e] Yuichiro Yamashiro[f] Maria Yarmolinskaya[g] Berthold Koletzko[h]

[a]University of Milan/ASST Fatebenefratelli Sacco, Milan, Italy; [b]University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; [c]Çukurova University, Adana, Turkey; [d]Ain Shams University, Cairo, Egypt; [e]University of Western Australia/Telethon Kids Institute, Perth, Subiaco, WA, Australia; [f]Juntendo University, Tokyo, Japan; [g]The Research Institute of Obstetrics, Gynaecology and Reproductive Medicine, Saint Petersburg, Russia; [h]LMU, Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany

Keywords
Micronutrients · Pregnancy · Early nutrition programming · Consensus report

Abstract
Background: Nutrition status prior to conception and during pregnancy and infancy seems to have an influence on the disease risk in adulthood (early nutrition/developmental programming). We aimed to review the current knowledge on the role of micronutrients in early nutrition programming and its implications for healthcare. ***Summary of Findings:*** Globally and even in high-income countries where a balanced diet is generally accessible, an inadequate maternal micronutrient status is common. This may induce health problems in the mother and foetus/newborn both immediately and in later life. Pregnant women and those who may become pregnant should aim to achieve a satisfactory micronutrient status from a well-balanced diet, and where necessary from additional supplements. ***Key Messages:*** We emphasise the need for a call to action for healthcare providers and policymakers to better educate women of child-bearing age regarding the short- and long-term benefits of an appropriate micronutrient status. The role of micronutrient status in early nutrition programming needs to be emphasized more to address the still limited awareness of the potential long-term health repercussions of suboptimal micronutrient supply during pregnancy.

KARGER

E-Mail karger@karger.com
www.karger.com/anm

Irene Cetin
Department of Biomedical and Clinical Sciences L. Sacco
University of Milan
Via G.B. Grassi 74, IT–20129 Milan (Italy)
E-Mail irene.cetin@unimi.it

Introduction

The "Developmental Origins of Health and Disease" or "Early Metabolic Programming" paradigm asserts that environmental factors including nutrition during pre- and postnatal phases of human development have a significant impact on health in adult life [1–4]. Retrospective human observational studies and experimental animal studies provide supportive evidence for this concept, demonstrating that events and exposures during critical windows of development from conception (or even before) through early childhood can significantly alter both immediate and long-term health [3, 5, 6]. More recently, additional evidence is contributed by randomized controlled intervention trials [7–12].

Early nutrition is one of the fundamental early exposures with the capacity to influence the development and subsequent function of virtually all body systems, including programming of metabolism, immune development, neurodevelopment and several other physiological processes. Here, we use the term "nutrition programming", as defined before (e.g., [2, 13, 14]), recognising these broad-ranging consequences. This is reflected in the increasing evidence that early nutritional patterns have long-term multisystem effects on health and risk of common non-communicable diseases (e.g., obesity and metabolic disease, immune diseases, and an extensive range of inflammatory and degenerative diseases) across the life course [14–16].

In pregnant women, micronutrient requirements increase more than the dietary energy requirements [6, 17]. Micronutrients constitute essential vitamins and minerals that must be derived from the diet to sustain virtually all vital cellular and molecular functions [18]. Inadequate maternal micronutrient status has significant potential to adversely affect many developmental processes in the foetus and in the breastfed infant, with both immediate and longer-term consequences. Interventions that prevent or reverse effects of adverse early nutrition programming could have huge implications for improving the health of future generations [13].

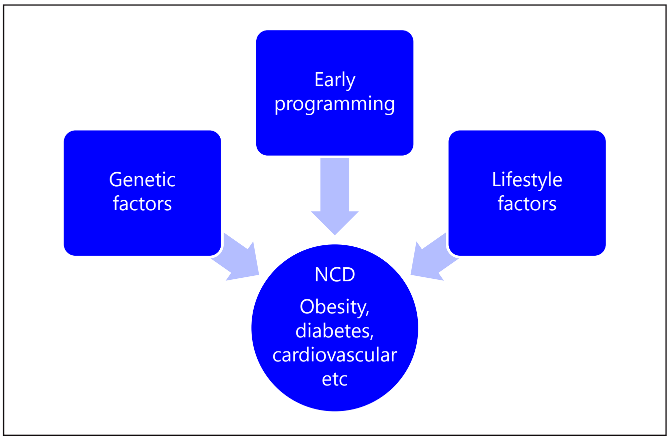
To review and discuss this topic, an international group of experts in the field met in Frankfurt, Germany on November 30, 2017. The major objective of the meeting was to review the current knowledge on the role of micronutrients in early programming and to discuss its implications for healthcare providers caring for pregnant and breastfeeding women, and for women who may become pregnant. Here we provide a summary of key information and conclusions in the format of a narrative review.

Early Nutrition Programming: The Concept

There is accumulating evidence that environmental cues during sensitive periods of early development modify the effects of the genome on phenotype [19]. This has been the basis of increasing focus on "the first thousand days" of life – arbitrarily defined as the time between conception and the end of a child's second year – as a period of significant "development plasticity". During this period, phenotypic development is more susceptible to change in response to environmental factors, although there is also evidence that (a) nutritional status before conception is also important, and (b) there is ongoing plasticity (albeit more limited) beyond this period [19, 20]. Early nutrition is arguably one of the most significant environmental determinants of an offspring's cell structure, epigenome, metabolome, hormones and microbiome [16, 19]. Epigenetic modification of gene expression could be one of the key pathways through which early nutrition may modify the developing phenotype, thereby inducing powerful effects on long-term health trajectories and disease risk [2, 20]. Epigenetics refers to heritable modifications in gene expression not caused by changes in DNA nucleotide sequence but by biochemical DNA modifications determining whether a gene is expressed or not [2, 21]. The most studied epigenetic modifications include histone modification, non-coding RNAs and DNA methylation [20]. Nutritional effects on the latter have been documented and represent a logical mechanism to explain the relationship between early nutrition and long-term health [2, 14, 16, 22]. While the concept of early nutrition programming and the long-term repercussions has been widely accepted by the scientific community [16, 23], this concept is still largely unknown to many women and healthcare providers.

Early nutrition status can clearly be beneficial or harmful to the child. While an adequate maternal perinatal nutrient status exerts favourable effects, inadequate environmental factors (including inadequate nutrition) may adversely affect early nutrition programming with a negative impact on later life. For instance, there is general consensus that the susceptibility of an individual to develop non-communicable diseases, such as obesity and associated disorders (e.g., diabetes, hypertension, cardiovascular diseases) during lifetime is – apart from genetic and lifestyle risk factors – influenced by adverse early metabolic programming leading to permanent alterations in the body's metabolic pathways (Fig. 1) [13, 16, 24].

Regarding the impact of early environmental exposures on the onset of obesity, detailed military records tak-



Color version available online

Fig. 1. The long-term risk of NCD is influenced by genetics, current lifestyle, and early programming in the perinatal period. NCD, non-communicable diseases.

en during the "Dutch famine" in the winter of 1944 have provided invaluable insights. These records showed that maternal exposure to famine during the first 2 trimesters of pregnancy led to a low birth weight and a significantly higher risk of obesity in male offspring in later life compared with normal eating pregnant women [25]. Similar effects were observed in Austria where 3 hunger periods were observed over the course of the twentieth century. These periods corresponded to subsequent spikes in diabetes prevalence in their male and female children [26]. However, not only undernutrition but also maternal obesity and overfeeding have been associated with an increased risk of later metabolic diseases in the offspring [19, 20, 27]. In addition, trans-generational transmission of obesity has been observed, with intrauterine overfeeding (i.e., intrauterine exposure to an excessive foetal supply of glucose or fatty acids) during the period of development plasticity as a contributing factor [19].

These observations illustrate that different stimuli (undernutrition/overfeeding) during the critical periods of early development may be involved in the pathogenesis of adult obesity. The concept of early nutrition programming provides an explanation for this phenomenon, thereby supporting the existence of epigenetic processes which affect gene expression in response to nutritional factors acting during early phases of human development. Other cues that can induce epigenetic responses include maternal hyperglycaemia or imbalance of nutrients that are involved in the methylation cycle [28]. Thus, maternal perinatal nutrition appears to be critical in this context; it influences whether early nutrition programming has either beneficial or adverse long-term consequences to the child.

Nutrient Supply and Early Programming

The importance of dietary habits during pregnancy and breastfeeding as well as in the pre-conceptional period has been widely acknowledged [6]. Consumption of a varied and balanced diet, as evidenced for the "New Nordic Diet" [29] or Mediterranean-type diets [30], has been associated with maternal well-being and a favourable pregnancy outcome, and with the offspring's long-term health. It has been shown that macro- and micronutrients are direct regulators of DNA stability and may have an impact on phenotype modifications by influencing epigenetic processes [31, 32].

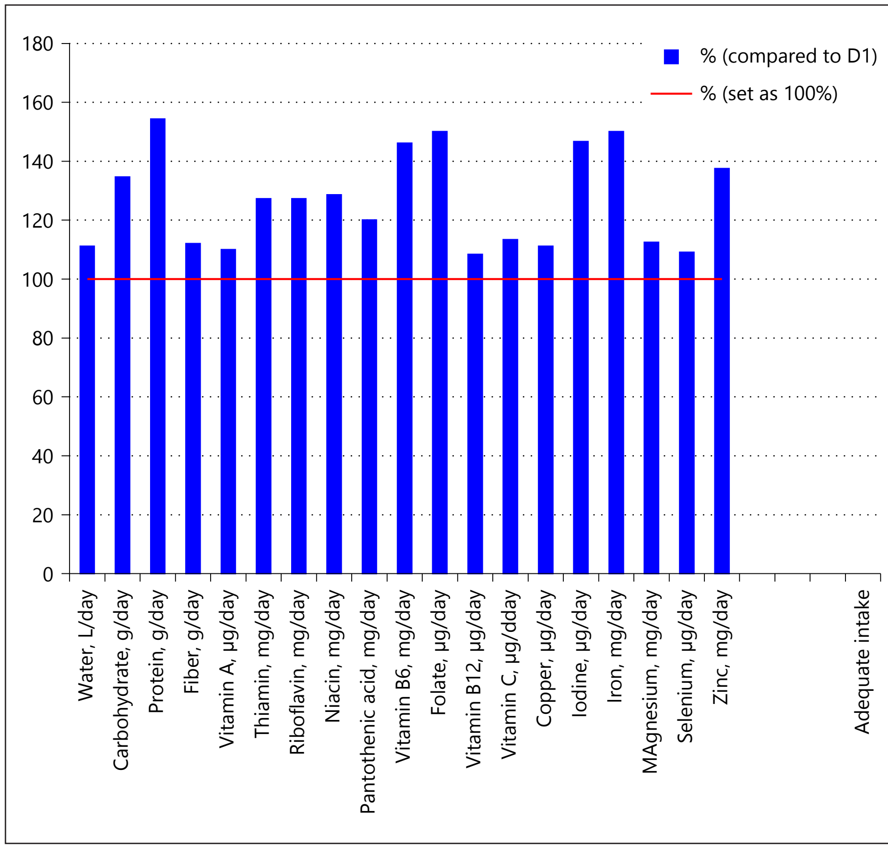
Nutritional requirements increase markedly during pregnancy, while some micronutrient requirements increase more than the energy needs (Fig. 2) [6, 17, 33]. Even in developed countries, where a balanced diet is accessible, micronutrient inadequacies are common due to a general switch to high-fat and low-quality diets (e.g., in highly processed products rich in salt, sugar and saturated fats), with frequently suboptimal intake particularly of iron, iodine, folate, vitamin D, vitamin B_{12} and docosahexaenoic acid (DHA) [33, 34]. It is known that low intakes of these micronutrients are of significant clinical relevance in pregnant women because they can lead to health problems in the mother and foetus/newborn [6, 28, 35]. Also during lactation, there is an increased need for some micronutrients (e.g., iodine and iron) [36, 37]. Of critical concern are the high needs of folic acid and iodine before and during pregnancy which generally are not provided by a well-balanced diet alone [17]. In fact, many countries now fortify the food supply (usually breads) with iodine and/or folate, partly to address the higher requirements during pregnancy and lactation.

It has been suggested that zinc, magnesium and chromium may exert epigenetic effects by reducing or increasing the methylation level at the promoter region of some genes [20]. A recent randomized controlled trial providing the omega-3 polyunsaturated fatty acid (n-3 PUFA) DHA to pregnant women reported differences in methylation in some DNA regions in their children relative to a control group [38].

Micronutrient Supply during Pregnancy

A recent meta-analysis evaluated the benefits of oral multiple micronutrient supplementation during pregnancy on maternal, foetal and infant health outcomes [39]. Data were evaluated from 17 trials involving

Ann Nutr Metab 2019;74:269–278
DOI: 10.1159/000499698



Color version available online

Fig. 2. Reference nutrient intake for pregnant women expressed as percentage of reference intake values for non-pregnant women (institute of medicine). D1, beginning of pregnancy; 100%, recommended daily allowance for non-pregnant women.

137,791 women. Fifteen of these 17 trials were carried out in low and middle-income countries. It was found that pregnant women who received multiple micronutrient supplementation had fewer low birth-weight babies and small-for-gestational-age babies than pregnant women who received only iron, with or without folic acid. The results from this meta-analysis underscore the benefits of multiple micronutrient supplements on pregnancy outcomes, at least in countries with a high incidence of low birth weight or small-for-gestational age babies. There is a need to understand more about whether micronutrient supplementation could improve outcomes in situations where it occurs in conjunction with maternal obesity/energy excess.

In one study, more than 2,000 children were followed up to study their cognitive development at 9–12 years of age [40, 41]. It was shown that maternal perinatal supplementation with multiple micronutrients had long-term benefits for child cognitive development at 9–12 years of age. The effect on procedural memory was significantly more pronounced compared with children receiving iron/folic acid supplementation only [41], thereby providing additional evidence that maternal micronutrient interventions might have long-term effects on the offspring beyond the neonatal period. The observed superior benefits with the multiple micronutrient intervention might be explained by a more complete rectification of (hidden) multiple micronutrient inadequacies in the mother.

In another meta-analysis, the micronutrient intake by pregnant women was analysed for USA/Canada, the UK, Europe, Australia/New Zealand and Japan. Folate, iron and vitamin D intake was consistently below nutrient intake recommendations in each region/country, while calcium intake was below the national recommendations in all regions/countries except for Europe [33, 42]. Multiple micronutrient supplementation during the perinatal period may help to achieve an optimized micronutrient status. However, supplements are not a substitute for a healthy diet [35]. Micronutrient supplementation should always be combined with consumption of a well-balanced diet. Adequate intake of sea fish, fruit and vegetables in the diet are important to ensure that all nutrients are consumed in sufficient but not excessive quantities. Pregnant women who are vegans or vegetarians need specific counselling because vegans always require supplementation of vitamin B_{12} and possibly additional nutrients, and also vegetarians should consider improving the intake of critical micronutrients [17]. Moreover, women at risk of gastrointestinal mal-absorption are candidates for zinc supplementation [43].

Although international guidelines support the supplementation of folic acid and other micronutrients (e.g., [44]), most of the current guidance for pregnant women and for young children does not take into account the long-term programming consequences of early nutrition [16]. In addition, nutrition and understanding of the developmental origins of disease is largely absent from university syllabuses [45]. There is a general lack of awareness by many healthcare providers of the potential benefits of micronutrient supplementation in pregnancy and during the pre-conceptional period. Particularly, its role in early nutrition programming is largely unknown. Thus, addressing unmet educational needs is of critical importance.

Micronutrient Intake during Pregnancy: Regional Differences

The intake of perinatal micronutrients from diet, fortified foods and supplements varies considerably between different regions of the world, even among industrialized countries. For instance, the average intake of folate was between 13 and 63% lower than recommended in a systematic review of 62 studies in pregnant women from developed countries [42]. Designing a multiple micronutrient supplement that fits for every population is challenging because each region has its own unique characteristics and specific needs. For example, in parts of Africa and Asia, mothers are typically younger than in other areas that may influence the type and quantity of micronutrients needed [45]. Six members of the expert panel (from Australia, Egypt, Germany, Japan, Russia and Turkey) presented some peculiarities/issues and national guidelines with regard to perinatal micronutrient intakes/recommended supplementation in their countries.

Australia

In Australia, national guidelines are set by the National Health and Medical Research Council and Food Standards of Australia and New Zealand. While consumption of dietary supplements during pregnancy and breastfeeding has become increasingly popular in Australia (up to 90%), less do so in the pre-conceptional period, and frequently maternal micronutrient intake is below the recommended daily intake quantity [46]. Folic acid supplementation is recommended, with at least 500 µg per day advised from 1 month before conception to 3 months after conception. As a national initiative, routine folic acid fortification of breads and cereals was introduced in Australia in 1996; this led to a 35–45% reduction in neural tube defects. Iodine supplementation is recommended at a daily dose of 150 µg pre-pregnancy, during pregnancy and while breast-feeding, owing to its importance in brain development. A mandatory iodine fortification of bread was introduced in 2009 in Australia. Overall, there was an improvement in the iodine status of pregnant and breastfeeding women, but iodine supplementation may still be required [47, 48]. It has been reported that South Australian pregnant women from a socially disadvantaged background did not reach levels compatible with iodine sufficiency following the mandatory iodine fortification of bread [49]. While iron is included in many over-the-counter pregnancy supplements, specific supplementation is generally only recommended if depletion has been identified. Vitamin B_{12} and calcium supplementation are considered in at-risk groups, such as vegan, vegetarians or those avoiding animal or dairy products for other reasons. While vitamin D supplementation is also recommended in groups at high risk of deficiency (such as veiled or dark-skinned women), there has been a significant increase in vitamin D supplementation in Australia, almost tripling between 2000 and 2010 [50]. Despite abundant sun shine, vitamin D deficiency is now commonplace in pregnant women [51–53] with rates of vitamin D deficiency (25-hydroxyvitamin D levels <50 nmol/L) of 14–36% in studies of predominantly white Caucasian women [54, 55]. This highlights the need for clinicians to be aware of the major contributing factors to vitamin D status in pregnant women to provide appropriate screening and advice around supplementation and aid in preventing vitamin D deficiency [55, 56].

In Australia, allergic disposition is a significant issue, including a striking increase in infant allergic diseases such as food allergy and eczema in the last decade [57, 58]. While this is likely to be multifactorial, there has been interest in the role of specific nutrients, such as the changes in vitamin D, folate and n-3 PUFA status based on the documented immunomodulatory properties of these nutrients, as discussed in detail elsewhere [59, 60]. Although there are no specific recommendations for allergy prevention with regard to specific nutrients at this stage, there is the need for a better understanding of nutritional programming of immune health, nutritional epigenetics and other biological processes sensitive to nutritional exposures in early life. This may lead to dietary strategies that provide more tolerogenic conditions during early immune programming and reduce the burden of many inflammatory diseases, not just allergy.

Egypt

A major nutritional problem in Egypt is the high proportion of obese or overweight adults and adolescents, while at the same time malnutrition continues to exist, inducing a significant double burden of both over- and undernutrition [61, 62]. Approximately one third of women aged 15–49 years and 30% of pregnant women are affected by iron-deficiency anaemia (IDA) [63]. This is related to a high consumption of carbohydrates and non-animal source proteins that has been observed over the last 2 decades, with cereals being the main source of energy in the Egyptian diet, and a low intake of foods providing sufficient amounts of iron with high bioavailability [64, 65]. Moreover, the intake of vitamin A, vitamin D, calcium, iodine, selenium and zinc is insufficient across the Egyptian population [61, 66]. To address these issues, several governmental and non-governmental programmes and initiatives have been rolled out (e.g., food fortification, school-feeding and micronutrient supplementation programmes), but effects have been suboptimal so far, mainly due to a lack of coordinated, integrated planning and implementation.

In particular, pregnant women living in rural areas frequently do not adhere to micronutrient supplementation recommendations due to lack of knowledge of its importance, and due to cost constraints [64].

In Egypt, there is an urgent need for a better coordination of ongoing programmes to raise the awareness among women and health care professionals concerning the importance of an adequate perinatal micronutrient status and the risks of overweight pregnancy to the mother and her child, and to implement effective prevention strategies.

Germany

In Germany, national recommendations on diet in pregnancy are provided by the government supported national network "A Healthy Start into Life" [17] and the German Society for Nutrition (DGE) [67]. Both recommend that in addition of a balanced, folate rich diet, a supplement with 400 μg/day folic acid is taken for at least 4 weeks prior to conception and continuing during the first trimester. During pregnancy a supplement with iodine (100 μg/day) and for those women who do not obtain regular sunshine exposure also with vitamin D (20 μg/day) are recommended. Women are advised to achieve an average daily intake of 200 mg DHA/day by eating 2 portions of marine fish per week including at least one portion of oily fish; women without a regular fish intake should take a daily supplement with the 200 mg DHA [17]. Iron supplementation in higher dosages is only recommended on an individual basis based on medical advice after laboratory assessment of haemoglobin and preferably also ferritin. Women following vegetarian and vegan diets are advised to obtain individual medical evaluation and counselling, and particularly for vegan women it is strongly recommended that they take a daily supplement with vitamin B_{12} and preferably also other micronutrients to prevent adverse effects of the restricted diet on the child [17].

Folic acid status is also considered important in the context of fertility. It has been suggested that higher plasma homocysteine levels are associated with the risk of anovulation and that lowering homocysteine with folic acid through diet or supplementation improves ovulatory function [68]. In addition, fertility treatments are thought to be more effective when folic acid is taken, leading to better progesterone levels and a positive correlation with conception rate [69]. Women with impaired ovulatory function and those scheduled for intracytoplasmic sperm injection may therefore represent an important target group for micronutrient supplementation. This may be inferred from previous double-blind, controlled studies, which documented higher pregnancy rates among users of micronutrient supplements either with or without fertility disorders [70, 71].

Japan

In the year 2000, the Japanese government introduced the recommendation for folic acid supplementation in women who may become pregnant. Nevertheless, the incidence of spina bifida cases increased significantly in recent years [72]. This is a result of the low intake of folic acid among Japanese pregnant women; even when taken, folic acid supplementation is typically not consumed as recommended. Only a small number of women (<30%) initiate folic acid supplementation in the pre-conceptional period [73]. The trend is not limited to folic acid, the average intake of vitamins C and D, iron, calcium and magnesium in pregnancy are also significantly below the recommended amounts [74]. A shift in dietary habits has been observed in Japan in recent years; vegetable intake is decreasing, with now only 17.5% of Japanese women aged 20–39 years consuming the recommended daily quantities of vegetables [74]. Moreover, the proportion of underweight women (BMI <18.5) is steadily rising, particularly in women aged 20–29 years, to recently 22.5% of this age group [74]. Consequently, the incidence of infants with low birth weight is increasing in Japan. The proportion of newborns weighing <2.5 kg is significantly higher in Japan (9.6%) than the average of industrialized countries (6.6%) [75].

Russia

Russian national nutrition guidelines recommend that all women who plan to get pregnant take folic acid (400–800 μg per day from 3 months preconception to at least 3 months after conception) and iodine during pregnancy (150 μg per day) [76]. In areas where iodine deficiency is endemic (95% of the territory of the Russian Federation), higher iodine doses should be ingested (up to 250 μg per day) [76]. Only 19% of women aged 20–45 years have adequate iron stores [77]. For women at risk of IDA or living in a region where IDA prevalence is above 20%, iron supplementation (60 mg per week given on an intermittent 3-monthly schedule, i.e., 3-month treatment/3-month break) is advised [76]. The latter recommendation applies for the majority of the Russian population. Moreover, it is advised that women planning to conceive take vitamin D at daily doses of 600–800 IU to be increased to 800–1,200 IU per day during pregnancy [76]. Vitamin D deficiency is endemic in Russia due to generally insufficient sunlight exposure [78]. Finally, all women are also encouraged to take omega-3 DHA at a dose of 200–300 mg/day during the pre-conceptional period and throughout pregnancy to support normal development of the foetus' brain, eyes and immune system. Despite these guidelines, only 9% of Russian women take micronutrients during pregnancy planning, and approximately 75% of pregnant women are affected by micronutrient deficiency [76, 79].

Turkey

In Turkey, the national maternal nutrition guidelines are broadly similar to the International Federation of Gynaecology and Obstetrics (FIGO) recommendations [28]. During the pre-conceptional period, folic acid supplementation is advocated, and during pregnancy, folic acid, n-3 PUFAs and iron supplements are recommended [80]. In Turkey, not many people eat fish on a regular basis [81]. Therefore, it is considered important to provide an n-3 PUFA (e.g., DHA) supplement to pregnant women [80].

In the Turkish population, certain groups need special attention. Adolescent pregnancies are observed rather frequently because women get married at a younger age compared with women in Western Europe [82]. This may have an impact on micronutrient requirements, but the micronutrient status of young and adolescent mothers has not been well studied [45]. A relatively high proportion of Turkish women follow a vegetarian or vegan diet with an increased risk of iron and vitamin B_{12} deficiencies. Approximately 34% of Turkish pregnant women have anaemia [83].

General Conclusions and Recommendations

The review of the situation in selected countries indicates that all countries face challenges in achieving an adequate micronutrient status of women before and during pregnancy and during lactation that would provide optimal promotion of maternal and child health. There is considerable variation in national nutrient intake recommendations and particularly in the pattern and prevalence of suboptimal or deficient status of specific nutrients.

This group of authors recommends that national recommendations on nutrition and lifestyle before and during pregnancy should be harmonised as much as possible with the global recommendations of FIGO [28], unless country-specific conditions (e.g., regarding documented nutritional status or established general food fortification strategies) require specific deviations from the FIGO recommendations.

The importance of maternal nutrition before and during pregnancy not only for her own health, but also for the health and development of her child until adulthood and old age is increasingly recognised among the scientific and medical community, and among women. Early nutrition programming is influenced by maternal nutrition before and during pregnancy and during lactation. An adequate supply of micronutrients and of omega-3 DHA is particularly important, with an impact on the incidence of congenital birth defects, anaemia and early premature birth, normal brain and neural tissue development, and the child's allergy risk.

Health care professionals should become more proactive in supporting women before and during pregnancy to follow a balanced nutrient-dense diet with a limited glycaemic load and without an excessive energy intake through information and practical advice. Particular attention should be directed to the selection of foods that are good sources of micronutrients and of omega-3 DHA.

In addition to a well-balanced diet, all women are advised to take supplements with folic acid starting at

Ann Nutr Metab 2019;74:269–278
DOI: 10.1159/000499698

least one month prior to conception and continuing through the first trimester, and with iodine during pregnancy. Supplementation choices of further micronutrients and of omega-3 DHA should be considered depending on the situation of the population and the individual woman.

Given the general lack of awareness of the potential benefits of micronutrient and DHA supplementation in women before and during pregnancy among healthcare providers caring for pregnant women, and among women, sharing of evidence-based information and target education of healthcare professionals clearly needs to be enhanced. One opportunity is the use of interactive digital educational programmes such as the Early Nutrition eAcademy (https://enea.med.lmu.de/), which also offers a module focussed on micronutrient needs. These activities might be enhanced by messages through the mass media to the general public and by implementing the subject in medical school syllabuses.

As a first step, healthcare professionals, from junior doctors to specialists, need to be better educated on the role of nutrition during pregnancy in laying the foundations for long-term health. As a second step, healthcare providers have to adequately convey this information to the target population. Each stakeholder should distribute clear messages that women understand the value of an adequate micronutrient status for her own health and the short- and long-term health of her baby.

The intake of perinatal micronutrients varies between different regions of the world, each with unique challenges and needs. Therefore, the most appropriate supplement regimen or supplement formulation needs to be tailored according to local requirements. The same applies to public awareness programmes because of cultural differences and varying levels of literacy.

Recommendations for Clinical Practice

– Assess all women who may become pregnant and are pregnant for a potential risk of inadequate nutrition.

– Counsel women on optimal dietary choices and its importance for maternal and child health, and on additional supplementation when needed.

Disclosure Statement

All authors have received financial support for participating in the related workshop. The authors have no ethical conflicts to disclose.

Funding Source

Bayer Consumer Care AG organized and funded the expert panel meeting and also provided editorial support in the preparation of this position paper (by Edgar A. Mueller, 3P Consulting).

References

1 Barker DJ. The origins of the developmental origins theory. J Intern Med. 2007 May; 261(5):412–7.
2 Koletzko B. The concept of early nutrition programming. Mini-Symposium “Early Nutrition Programming of Long-Term Health”. December 1st 2014, Warsaw, Poland (http://fundacjanutricia.pl/wp-content/uploads/2014/12/Ksi%C4%85%C5%BCka-abstrakt%C3%B3w.pdf)
3 Mandy M, Nyirenda M. Developmental Origins of Health and Disease: the relevance to developing nations. Int Health. 2018 Mar; 10(2):66–70.
4 Bischoff AR, Cunha FD, Dalle Molle R, Maróstica PJ, Silveira PP. Is willingness to exercise programmed in utero? Reviewing sedentary behavior and the benefits of physical activity in intrauterine growth restricted individuals. J Pediatr (Rio J). 2018 Nov - Dec;94(6):582–95.
5 Adair LS. Long-term consequences of nutrition and growth in early childhood and possible preventive interventions. Nestle Nutr Inst Workshop Ser. 2014;78:111–20.
6 Marangoni F, Cetin I, Verduci E, Canzone G, Giovannini M, Scollo P, et al. Maternal diet and nutrient requirements in pregnancy and breastfeeding. An Italian consensus document. Nutrients. 2016 Oct;8(10):E629.
7 De-Regil LM, Fernández-Gaxiola AC, Dowswell T, Peña-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2010 Oct;(10):CD007950.
8 Lassi ZS, Salam RA, Haider BA, Bhutta ZA. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. Cochrane Database Syst Rev. 2013 Mar;(3):CD006896.
9 Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al.; LIMIT Randomised Trial Group. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. BMJ. 2014 Feb;348:g1285.
10 Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, et al.; European Childhood Obesity Trial Study Group. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. Am J Clin Nutr. 2014 May;99(5):1041–51.
11 Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L, et al.; UPBEAT Trial Consortium. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2015 Oct;3(10):767–77.
12 Totzauer M, Luque V, Escribano J, Closa-Monasterolo R, Verduci E, ReDionigi A, et al.; European Childhood Obesity Trial Study Group. Effect of lower versus higher protein content in infant formula through the first year on body composition from 1 to 6 years: follow-up of a randomized clinical trial. Obesity (Silver Spring). 2018 Jul;26(7):1203–10.
13 Koletzko B, Brands B, Demmelmair H; Early Nutrition Programming Project. The Early Nutrition Programming Project (EARNEST): 5 y of successful multidisciplinary collaborative research. Am J Clin Nutr. 2011 Dec;94(6 Suppl):1749S–53S.

14 Koletzko B, Brands B, Poston L, Godfrey K, Demmelmair H; Early Nutrition Project. Early nutrition programming of long-term health. Proc Nutr Soc. 2012 Aug;71(3):371–8.
15 Tounian P. Programming towards childhood obesity. Ann Nutr Metab. 2011;58(s2 Suppl 2):30–41.
16 Koletzko B, Brands B, Grote V, Kirchberg FF, Prell C, Rzehak P, et al.; Early Nutrition Programming Project. Long-term health impact of early nutrition: the power of programming. Ann Nutr Metab. 2017;70(3):161–9.
17 Koletzko B, Bauer CP, Bung P, Cremer M, Flothkötter M, Hellmers C, et al. German national consensus recommendations on nutrition and lifestyle in pregnancy by the 'Healthy Start - Young Family Network'. Ann Nutr Metab. 2013;63(4):311–22.
18 Bailey RL, West KP Jr, Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab. 2015;66 Suppl 2:22–33.
19 Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, et al. The Power of Programming and the EarlyNutrition project: opportunities for health promotion by nutrition during the first thousand days of life and beyond. Ann Nutr Metab. 2014;64(3-4):187–96.
20 Lorite Mingot D, Gesteiro E, Bastida S, Sánchez-Muniz FJ. Epigenetic effects of the pregnancy Mediterranean diet adherence on the offspring metabolic syndrome markers. J Physiol Biochem. 2017 Nov;73(4):495–510.
21 Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. Semin Reprod Med. 2009 Sep;27(5):351–7.
22 Rzehak P, Covic M, Saffery R, Reischl E, Wahl S, Grote V, et al. DNA-methylation and body composition in preschool children: epigenome-wide-analysis in the European Childhood Obesity Project (CHOP)-Study. Sci Rep. 2017 Oct;7(1):14349.
23 Berti C, Agostoni C, Davanzo R, Hyppönen E, Isolauri E, Meltzer HM, et al. Early-life nutritional exposures and lifelong health: immediate and long-lasting impacts of probiotics, vitamin D, and breastfeeding. Nutr Rev. 2017 Feb;75(2):83–97.
24 Rauschert S, Kirchberg FF, Marchioro L, Koletzko B, Hellmuth C, Uhl O. Early programming of obesity throughout the life course: A metabolomics perspective. Ann Nutr Metab. 2017;70(3):201–9.
25 Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med. 1976 Aug;295(7):349–53.
26 Thurner S, Klimek P, Szell M, Duftschmid G, Endel G, Kautzky-Willer A, et al. Quantification of excess risk for diabetes for those born in times of hunger, in an entire population of a nation, across a century. Proc Natl Acad Sci USA. 2013 Mar;110(12):4703–7.
27 Rajia S, Chen H, Morris MJ. Maternal overnutrition impacts offspring adiposity and brain appetite markers-modulation by postweaning diet. J Neuroendocrinol. 2010 Aug;22(8):905–14.
28 Hanson MA, Bardsley A, De-Regil LM, Moore SE, Oken E, Poston L, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". Int J Gynaecol Obstet. 2015 Oct;131 Suppl 4:S213–53.
29 Hillesund ER, Bere E, Haugen M, Øverby NC. Development of a New Nordic Diet score and its association with gestational weight gain and fetal growth - a study performed in the Norwegian Mother and Child Cohort Study (MoBa). Public Health Nutr. 2014 Sep;17(9):1909–18.
30 Timmermans S, Steegers-Theunissen RP, Vujkovic M, den Breeijen H, Russcher H, Lindemans J, et al. The Mediterranean diet and fetal size parameters: the Generation R Study. Br J Nutr. 2012 Oct;108(8):1399–409.
31 Sebert S, Sharkey D, Budge H, Symonds ME. The early programming of metabolic health: is epigenetic setting the missing link? Am J Clin Nutr. 2011 Dec;94(6 Suppl):1953S–8S.
32 Cetin I, Mandò C, Calabrese S. Maternal predictors of intrauterine growth restriction. Curr Opin Clin Nutr Metab Care. 2013 May;16(3):310–9.
33 Parisi F, Laoreti A, Cetin I. Multiple micronutrient needs in pregnancy in industrialized countries. Ann Nutr Metab. 2014;65(1):13–21.
34 Berti C, Biesalski HK, Gärtner R, Lapillonne A, Pietrzik K, Poston L, et al. Micronutrients in pregnancy: current knowledge and unresolved questions. Clin Nutr. 2011 Dec;30(6):689–701.
35 Milman N, Paszkowski T, Cetin I, Castelo-Branco C. Supplementation during pregnancy: beliefs and science. Gynecol Endocrinol. 2016 Jul;32(7):509–16.
36 Gónzalez-Iglesias H, de la Flor St Remy RR, López-Sastre J, Fernández-Colomer B, Ibánez-Fernández A, Solís G, et al. Efficiency of iodine supplementation, as potassium iodide, during lactation: a study in neonates and their mothers. Food Chem. 2012;133(3):859–65.
37 Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al.; Lancet Nutrition Interventions Review Group, the Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013 Aug;382(9890):452–77.
38 van Dijk SJ, Zhou J, Peters TJ, Buckley M, Sutcliffe B, Oytam Y, et al. Effect of prenatal DHA supplementation on the infant epigenome: results from a randomized controlled trial. Clin Epigenetics. 2016 Nov;8(1):114–26.
39 Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2017 Apr;4:CD004905.
40 Shankar AH, Jahari AB, Sebayang SK, Aditiawarman, Apriatni M, Harefa B, et al.; Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. Lancet. 2008 Jan;371(9608):215–27.
41 Prado EL, Sebayang SK, Apriatni M, Adawiyah SR, Hidayati N, Islamiyah A, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9-12 years in Indonesia: follow-up of the SUMMIT randomised trial. Lancet Glob Health. 2017 Feb;5(2):e217–28.
42 Blumfield ML, Hure AJ, Macdonald-Wicks L, Smith R, Collins CE. A systematic review and meta-analysis of micronutrient intakes during pregnancy in developed countries. Nutr Rev. 2013 Feb;71(2):118–32.
43 Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, et al. Zinc in early life: A key element in the fetus and preterm neonate. Nutrients. 2015 Dec;7(12):10427–46.
44 World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/handle/10665/250796/9789241549912-eng.pdf;jsessionid=CBCA599315066BB784966564DC26F365?sequence=1)
45 Krebs N, Bagby S, Bhutta ZA, Dewey K, Fall C, Gregory F, et al. International summit on the nutrition of adolescent girls and young women: consensus statement. Ann N Y Acad Sci. 2017 Jul;1400(1):3–7.
46 Livock M, Anderson PJ, Lewis S, Bowden S, Muggli E, Halliday J. Maternal micronutrient consumption periconceptionally and during pregnancy: a prospective cohort study. Public Health Nutr. 2017 Feb;20(2):294–304.
47 Huynh D, Condo D, Gibson R, Makrides M, Muhlhausler B, Zhou SJ. Comparison of breast-milk iodine concentration of lactating women in Australia pre and post mandatory iodine fortification. Public Health Nutr. 2017 Jan;20(1):12–7.
48 Condo D, Huyhn D, Anderson AJ, Skeaff S, Ryan P, Makrides M, et al. Iodine status of pregnant women in South Australia after mandatory iodine fortification of bread and the recommendation for iodine supplementation. Matern Child Nutr. 2017 Oct;13(4):e12410.
49 Clifton VL, Hodyl NA, Fogarty PA, Torpy DJ, Roberts R, Nettelbeck T, et al. The impact of iodine supplementation and bread fortification on urinary iodine concentrations in a mildly iodine deficient population of pregnant women in South Australia. Nutr J. 2013 Mar;12(1):32.
50 Bilinski K, Talbot P. Vitamin d supplementation in australia: implications for the development of supplementation guidelines. J Nutr Metab. 2014;2014:374208.

51 Bowyer L, Catling-Paull C, Diamond T, Homer C, Davis G, Craig ME. Vitamin D, PTH and calcium levels in pregnant women and their neonates. Clin Endocrinol (Oxf). 2009 Mar;70(3):372–7.
52 Teale GR, Cunningham CE. Vitamin D deficiency is common among pregnant women in rural Victoria. Aust N Z J Obstet Gynaecol. 2010 Jun;50(3):259–61.
53 Thomas SD, Fudge AN, Whiting M, Coates PS. The correlation between third-trimester maternal and newborn-serum 25-hydroxy-vitamin D in a selected South Australian group of newborn samples. BMJ Open. 2011 Jan;1(2):e000236.
54 Hart PH, Lucas RM, Walsh JP, Zosky GR, Whitehouse AJ, Zhu K, et al. Vitamin D in fetal development: findings from a birth cohort study. Pediatrics. 2015 Jan;135(1):e167–73.
55 Jones AP, Rueter K, Siafarikas A, Lim EM, Prescott SL, Palmer DJ. 25-hydroxyvitamin D status of pregnant women is associated with the use of antenatal vitamin supplements and ambient ultraviolet radiation. J Dev Orig Health Dis. 2016 Aug;7(4):350–6.
56 De Laine KM, Matthews G, Grivell RM. Prospective audit of vitamin D levels of women presenting for their first antenatal visit at a tertiary centre. Aust N Z J Obstet Gynaecol. 2013 Aug;53(4):353–7.
57 Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. Pediatr Allergy Immunol. 2011 Mar;22(2):155–60.
58 Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al.; HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011 Mar;127(3):668–76.e1.
59 Rueter K, Prescott SL, Palmer DJ. Nutritional approaches for the primary prevention of allergic disease: an update. J Paediatr Child Health. 2015 Oct;51(10):962–9.
60 McStay CL, Prescott SL, Bower C, Palmer DJ. Maternal folic acid supplementation during pregnancy and childhood allergic disease outcomes: A Question of Timing? Nutrients. 2017 Feb;9(2):E123.
61 World Health Organization. Regional Committee for the Eastern Mediterranean. Regional Strategy on Nutrition 2010-2019. EM/RC57/4; 2010 (http://applications.emro.who.int/docs/EM_RC57_4_en.pdf)
62 Ministry of Health and Population [Egypt], El-Zanaty and Associates [Egypt], and ICF International. 2015. Egypt Health Issues Survey 2015. Cairo, Egypt and Rockville, Maryland, USA: Ministry of Health and Population and ICF International (https://dhsprogram.com/pubs/pdf/FR313/FR313.pdf)
63 World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf;jsessionid=B7E9EF572996348C7BB4BD17984752C6?sequence=1)
64 Rezk M, Marawan H, Dawood R, Masood A, Abo-Elnasr M. Prevalence and risk factors of iron-deficiency anaemia among pregnant women in rural districts of Menoufia governorate, Egypt. J Obstet Gynaecol. 2015;35(7):663–6.
65 Tawfik AS, Hanna ET, Abdel-Maksoud AM. Anemia and iron deficiency anemia in Egypt. IOSR J Pharm. 2015;5(4):30–4.
66 Hwalla N, Al Dhaheri AS, Radwan H, Alfawaz HA, Fouda MA, Al-Daghri NM, et al. The prevalence of micronutrient deficiencies and inadequacies in the Middle East and approaches to interventions. Nutrients. 2017 Mar;9(3). pii:E229.
67 Deutsche Gesellschaft für Ernährung: Erste einheitliche Handlungsempfehlungen zur Ernährung in der Schwangerschaft. DGEinfo (12/2011) 184-187. (https://www.dge.de/ernaehrungspraxis/bevoelkerungsgruppen/schwangere-stillende/handlungsempfehlungen-zur-ernaehrung-in-der-schwangerschaft/) https://doi.org/10.3390/nu9030229.
68 Michels KA, Wactawski-Wende J, Mills JL, Schliep KC, Gaskins AJ, Yeung EH, et al. Folate, homocysteine and the ovarian cycle among healthy regularly menstruating women. Hum Reprod. 2017 Aug;32(8):1743–50.
69 Gaskins AJ, Mumford SL, Chavarro JE, Zhang C, Pollack AZ, Wactawski-Wende J, et al. The impact of dietary folate intake on reproductive function in premenopausal women: a prospective cohort study. PLoS One. 2012;7(9):e46276.
70 Czeizel AE, Métneki J, Dudás I. The effect of preconceptional multivitamin supplementation on fertility. Int J Vitam Nutr Res. 1996;66(1):55–8.
71 Westphal LM, Polan ML, Trant AS, Mooney SB. A nutritional supplement for improving fertility in women: a pilot study. J Reprod Med. 2004 Apr;49(4):289–93.
72 Kondo A, Morota N, Ihara S, Saisu T, Inoue K, Shimokawa S, et al. Risk factors for the occurrence of spina bifida (a case-control study) and the prevalence rate of spina bifida in Japan. Birth Defects Res A Clin Mol Teratol. 2013 Sep;97(9):610–5.
73 Sato Y, Nakanishi T, Chiba T, Umegaki K. [Attitudes of pregnant Japanese women and folic acid intake for the prevention of neural tube defects: a nationwide Internet survey]. Nihon Koshu Eisei Zasshi. 2014;61(7):321–32.
74 Ministry of Health. Labour and Work. Japan National Health and Nutrition Survey; 2013 (http://www.mhlw.go.jp/english/)
75 OECD Health Statistics 2015 (http://dx.doi.org/https://doi.org/10.1787/health-data-en.).
76 MARS. Harmonized protocol of the interdisciplinary association of specialists in reproductive medicine, Russia (MARS). Status-Praesens, Moscow; 2016 (http://www.kb51.ru/pdf/vv3.pdf)
77 Limanova OA, Torshin IY, Sardaryan IS, Kalacheva AG, Hababpashev A, Karpuchin D. Micronutrient supply and women's health: intellectual analysis of clinical and epidemiological data. Voprosyi ginekologii, akusherstva i perinatologii. 2014;13:5–15.
78 Karonova T, Andreeva A, Nikitina I, Belyaeva O, Mokhova E, Galkina O, et al. Prevalence of Vitamin D deficiency in the North-West region of Russia: A cross-sectional study. J Steroid Biochem Mol Biol. 2016 Nov;164:230–4.
79 Scheplyagina LA. Impact of the mother's zinc deficiency on the woman's and newborn's health status. J Trace Elem Med Biol. 2005;19(1):29–35.
80 Guidelines TD. Ministry of Health of Turkey Publication No: 1046, Ankara; 2016 (https://dosyasb.saglik.gov.tr/Eklenti/10922,17ocaktuberingilizcepdf.pdf?0)
81 Aydin H, Dilek MK, Aydin K. Trends in fish and fishery products consumption in Turkey. Turk J Fish Aquat Sci. 2011;11(3):499–506.
82 United Nations Population Fund Turkey. Child Marriage in Turkey. June 2014, Version 2 (https://eeca.unfpa.org/sites/default/files/pub-pdf/unfpa%20turkey%20overview.pdf)
83 World Health Organization. Nutrition Landscape Information System (NLiS). NLiS Country Profile 2018: Turkey (http://apps.who.int/nutrition/landscape/report.aspx?iso=tur)