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Original Article

Critical issues in setting micronutrient recommendations for pregnant women: an insight

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Abstract

The European Micronutrient Recommendations Aligned (EURRECA) project aims to provide standardized approaches to reveal and beneficially influence variability within the European Union in micronutrient recommendations for vulnerable population groups. Characterization of the 'vulnerability' together with the 'variability' of micronutrient needs represents the first step to creating guidelines for setting micronutrient recommendations within target populations. This paper describes some of the key factors and characteristics relevant to assess micronutrient requirements and formulate recommendations of micronutrients in pregnancy. Nutritional requirements during pregnancy increase to support fetal growth and development as well as maternal metabolism and tissue accretion. Micronutrients are involved in both embryonal and fetal organ development and overall pregnancy outcomes. Several factors may affect directly or indirectly fetal nourishment and the overall pregnancy outcomes, such as the quality of diet including intakes and bioavailability of micronutrients, maternal age, and the overall environment. The bioavailability of micronutrients during pregnancy varies depending on specific metabolic mechanisms because pregnancy is an anabolic and dynamic state orchestrated via hormones acting for both redirection of nutrients to highly specialized maternal tissues and transfer of nutrients to the developing fetus. The timing of prenatal intakes or supplementations of specific micronutrients is also crucial as pregnancy is characterized by different stages that represent a continuum, up to lactation and beyond. Consequently, nutrition during pregnancy might have long-lasting effects on the well-being of the mother and the fetus, and may further influence the health of the baby at a later age.

Keywords: EURRECA, pregnancy, vulnerability, recommendation, requirement, bioavailability, dietary factors, micronutrient intakes.

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Background

Nutrient recommendations are part of the basis for food policy and food-based dietary guidelines, and are used in nutrition labelling. The historical development of the concept of dietary recommendations for populations or groups has been reported by Aggett *et al.* (1997). This evolution happened as a consequence of the understanding of the role of nutrients not only in the avoidance of clinical deficiencies but also in the reduction of the risk of chronic degenerative diseases.

A large heterogeneity of micronutrient recommendations exists across Europe, both quantitatively and

Table 1. Recommendations of some micronutrients for pregnant women and their related footnotes within some European countries (adapted from the original tables in references)

	Vit A	Vit D	Vit B_{12}	Folate	Iodine	Zinc	Iron
			(μg day^{-1})			(mg day^{-1})	
United Kingdom (COMA 1991)	700	10	1.5[§]	300	140[§]	7[§]	14.8[§¶]
Italy (LARN 1996)	700	10[††]	2.2	400[††]	175	7	30[††]
Nordic countries (NNR 2004)	800	10	2.0	500	175	9[§§]	–[‡‡¶¶]
Spain (Moreiras *et al.* 2007)[†]	800	10	2.2	600[‡]	135	20	18
D-A-CH (2000)	1.1 mg RE	5	3.5	600	230 (CH: 200)	10	30

Nordic countries, Denmark, Finland, Iceland, Norway, Sweden; D-A-CH, Germany, Austria, Switzerland; RE, retinol equivalent; Vit D, 10 μg day^{-1} corresponds to 400 IU day^{-1}, 5 μg day^{-1} corresponds to 200 IU day^{-1}; [†]from the second half of pregnancy; [‡]first and second half of gestation; [§]no increment. [¶]Insufficient for women with high menstrual losses where the most practical way of meeting iron requirements is to take iron supplements. [††]Dietary supplements or fortified foods may be required. [‡‡]The composition of the meal influences the utilization of dietary iron. The availability increases if the diet contains abundant amounts of vitamin C and meat or fish daily, while it is decreased at simultaneous intake of e.g. polyphenols or phytic acid. [§§]The utilization of zinc is negatively influenced by phytic acid and positively by animal protein. The recommended intakes are valid for a mixed animal/vegetable diet. For vegetarian cereal-based diets, a 25–30% higher intake is recommended. [¶¶]Iron balance during pregnancy requires iron stores of approximately 500 mg at the start of pregnancy. The physiological need of some women for iron cannot be satisfied during the last two-thirds of pregnancy with food only, and supplemental iron is therefore needed.

qualitatively; therefore, a common agreement should be sought on the different uses and applications of nutrient recommendations, as critically discussed by Pijls *et al.* (2009). Table 1 collates differences in the recommendations of some micronutrients for pregnant women from several European countries. The European Micronutrient Recommendations Aligned (EURRECA) project aims at providing standardized approaches to reveal variability within the European Union in micronutrient recommendations for population groups (Doets *et al.* 2008), with particular interest in 'vulnerable populations'. 'Vulnerable groups' are defined as 'population groups in a healthy population having a higher requirement'.

Pregnant women are considered a 'vulnerable group', as their nutritional requirements increase to support fetal and infant growth and development as well as maternal metabolism and tissue accretion. The estimated average requirement (EAR) is the daily intake value that is estimated to meet this requirement, as defined by the specific indicator of adequacy, in half of the individuals in a life-stage or gender group (WHO/FAO 2004). The estimated total nutrient requirements during pregnancy can be derived from nutrients and energy accumulated in maternal tissues plus those necessary for products of pregnancy and lactation in addition to the baseline requirements for non-pregnant, non-lactating women. Determination of nutrient needs during pregnancy is a complex task because of the alteration of nutrient levels in tissues and fluids as a result of the hormone-induced changes in metabolism, shifts in plasma volume and changes in renal function as well as in patterns of urinary excretion.

When assessing micronutrient recommendations for pregnant women, besides physiological variation, environmental factors must be defined and explored. Macro-level factors such as socio-economic and political contexts, and food availability along with micro-level factors such as local cultural practices,

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Key messages

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norms, lifestyles, attitudes and beliefs influence food consumption (Pelto 1987; Hall Moran & Dykes 2009). 8 Moreover, application of any future nutritional guidelines should also consider new evidence for biological role of micronutrients.

The aim of this paper is to discuss the nutritional specificities of pregnant women and the approaches underlying the definition of micronutrient dietary reference values and recommendation, i.e. the physiological and environmental factors influencing the bioavailability of micronutrients in pregnancy.

This narrative review develops from several integrating meetings and activities within the EURRECA project through evidence-based opinion and explorative work (http://www.eurreca.org). 9 Publications were searched using electronic databases and websites, hand searching relevant journals, contact with experts. 10 The databases searched were Embase, Medline and PubMed databases, and Google-indexed scientific literature and periodics from on-line University of Milan Library Service. We used combinations of the following keywords: micronutrient, requirement, intake, supplement, status, malnutrition, deficiency, excess, overload, food, dietary patterns, pregnancy, pregnancy need, pregnancy health, pregnancy disease, pregnancy outcome, fetus, placenta, newborn and mother. Only human studies were considered, both original studies and reviews. Moreover, official and national documents were used.

Factors influencing micronutrient recommendations in pregnancy

> The physiological requirement for a nutrient should be the basis for calculating a reference intake. The ideal definition of a physiological requirement is the amount and chemical form of a nutrient that is needed systematically to maintain normal health and development without disturbance of the metabolism of any other nutrient. The corresponding dietary requirement would be the intake sufficient to meet the physiological requirement.
>
> (Aggett *et al*. 1997)

When assessing recommendations, quality of diet, genetics, physiological stress, pre-pregnancy body mass index, body composition, gestational weight gain, time of gestation, maternal age, lifestyle, socioeconomic status, culture, ethnicity, etc. must be taken into account. This means that the bioavailability of nutrients, depending not only on the composition of diet or the chemical form of the nutrient but also on the nutritional status or physiological stage, is a crucial issue.

Pregnancy physiological–metabolic factors

Pregnancy is an anabolic state in which the body undergoes significant physiological and anatomical changes (Munro & Eckerman 1998). Hormones act towards a redirection of nutrients to highly specialized maternal tissues (placenta and mammary gland) and for the transfer of nutrients to the developing fetus. Biochemical, metabolic and physiological adjustments of the maternal organism meet the extra demands of the developing fetus and placenta (Kalhan 2000; Lain & Catalano 2007; Carlin & Alfirevic 2008) and support the homeostasis of micronutrients such as iodine (Zimmermann 2009), iron (Milman 2006) and calcium (Kovacs 2008). Body composition changes dramatically with maternal fat accretion. Maternal fat storage increases in early to mid-gestation and, during late gestation, these maternal energy reserves are mobilized, following changes in maternal insulin production, to provide an increased supply of energy to the fetus. Improved availability of substrates and precursors for fetal–placental metabolism and hormone production is mediated through increments in dietary intake and endocrine changes that increase the availability of nutritional substrates (Weissgerber & Wolfe 2006).

Pregnancy is characterized by different stages that represent a continuum (Fig. 1) both in a life cycle context and from a nutritional point of view. In details, the first trimester is the time for the fetus when organogenesis (embryogenesis) takes place, and tissue patterns and organ systems are established; in the second trimester, the fetus undergoes major cellular adaptation and an increase in body size; during the third trimester, organ systems mature, and there is a significant increase in fetal body weight (Mullis & Tonella 2008). Nutritional deficiencies occurring during pregnancy might have long-lasting effects on both maternal and infantile and adult health. In par-

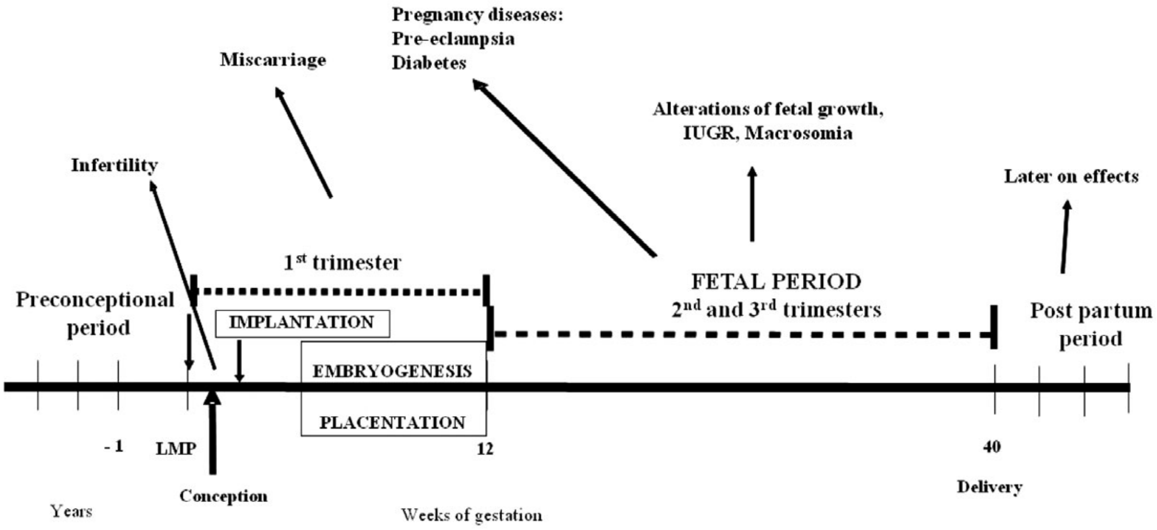

Fig. 1. Different pregnancy stages from the preconceptional to the post-partum period. Several specific malformations and pregnancy-related disorders may originate during each phase. LMP, last menstrual period. Adapted from Cetin *et al.* (2009). 54 55 58

ticular, the periconceptional period, which encompasses preconception, conception, implantation, placentation and embryo- or organogenesis, is a stage of pregnancy representing a critical step in determining fetal development (reviewed in Cetin *et al.* 2009). Later on, placental function regulates fetal growth and development (Desoye & Hauguel-De Mouzon 2007). Several fetal diseases originate in the placenta and develop only later on in the fetus (Pardi & Cetin 2006). The 'fetal' or 'early' origins of adult disease hypothesis suggests that environmental factors, particularly nutrition, act through the processes of developmental plasticity (i.e. the ability of the fetus to respond to environmental cues by choosing a trajectory of development that often offers an adaptive advantage) to alter the development of the organism to such an extent that affects its capacity to cope with the environment in adult life, and therefore influences disease risk in adult life (Gluckman *et al.* 2005; McMillen & Robinson 2005).

The main characteristics of pregnancy that need to be highlighted from the nutritional perspective are as follows:

1. Pregnancy is characterized by a three-compartment model, i.e. mother/placenta/fetus. Each of them has different metabolism; placenta transport function determines the composition of the umbilical cord blood providing nutrients and oxygen to the fetus to assure appropriate fetal growth (Cetin *et al.* 2005). Fetal growth is regulated by the balance between fetal nutrient demand and maternal–placental nutrient supply. Maternal nutrition and metabolism, utero-placental blood flow, size and transfer capabilities of the placenta all determine the maternal–placental supply of nutrients (Pardi & Cetin 2006).

2. Pregnancy is a dynamic state, during which adjustments in nutrient metabolism evolve continuously as the mother switches from an anabolic condition during early pregnancy to a catabolic state during late pregnancy (Catalano *et al.* 2002; Hauguel-de Mouzon *et al.* 2006). This switch is illustrated, e.g. in lipid metabolism going from fat deposition as a result of both hyperphagia and enhanced lipogenesis during the first and second trimesters to fat breakdown during the third trimester (Herrera 2000). Consequently, qualitative differences in dietary requirements exist during early and late pregnancy.

3. Maternal stores that have been developed before and throughout pregnancy will influence the composition of breast milk during lactation (Picciano 2003).

Period of gestation

Adequate maternal micronutrient status and intake prior to conception and throughout the entire pregnancy is critical to ensure satisfactory birth outcomes (reviewed in Picciano 2003 and Allen 2005). Timing of maternal nutritional intake and status impacting specifically and differently on the embryonal/fetal organ development, time of initiation and dose of prenatal supplementation influencing maternal micronutrient status, as well as the role of the interaction between the pre- and post-natal environment in determining final health outcomes, are important issues (Gardiner 2007). Preconceptional nutritional status appears to be crucial for an optimal onset and development of pregnancy (reviewed by Cetin *et al*. 2009), suggesting the importance of adequate micronutrient intake of all women of childbearing age. This may be, for instance, of particular concern for calcium; if adequate bone mass has not been accrued before pregnancy and the intake of calcium from maternal diet is low, calcium is taken from the maternal skeleton (Thomas & Weisman 2006).

Specifying the micronutrient recommendations for specific periods of gestation may improve the overall outcome of pregnancy. In this regard, mineral recommendations by WHO/FAO (2004) are separated for the first, second and third trimesters of pregnancy. Spain recommends increased intakes of calcium, iodine, magnesium, niacin and vitamin E from the second half of pregnancy and an increased folate intake in the first half of gestation (Moreiras *et al*. 2007). In the UK, increased thiamin intake is recommended for the last trimester of pregnancy only (COMA 1991). However, micronutrient recommendations in most European countries do not differentiate between specific periods of gestation.

Effect of prenatal micronutrients on pregnancy outcomes

The biological role and reliable functional markers or indicators of status of the micronutrients that are of considerable public health significance during pregnancy are shown in Table 2.

Increasing the intake of folic acid before and during the first weeks of pregnancy can reduce birth defects (MRC, 1991; Czeizel & Dudás 1992; Czeizel *et al*. 1999); hence, periconceptional folic acid supplements in doses of 4000 and 400 μg daily are recommended in addition to adequate dietary folate to prevent, respectively, recurrence and occurrence of neural tube defects (NTDs) (de Bree *et al*. 1997). Folate and/or vitamin B_6/B_{12} deficiencies as a result of deregulation of their normal metabolism and/or low dietary intake (reviewed in Steen *et al*. 1998, and Tamura & Picciano 2006) may induce elevation in plasma total homocysteine or hyperhomocysteinemia as a consequence of decrease in the methylation cycle. Some 'placenta events' are postulated to arise from deficiencies of either folate and/or vitamin B_{12} or defect within the methionine–homocysteine metabolic pathways (Goddijn-Wessel *et al*. 1996; Ray & Laskin 1999; Braekke *et al*. 2007; Dodds *et al*. 2008). Moreover, altered homocysteine metabolism leading to hyperhomocysteinemia has been proposed as the mechanism involved in NTDs (Locksmith & Duff 1998).

Prenatal vitamin A or beta-carotene supplementation or fortification may reduce maternal mortality in vitamin A-deficient mothers (West *et al*. 1999). Although an excessive intake has been shown to be teratogenic (McCaffery *et al*. 2003; Williamson 2006), adequate maternal vitamin A status is crucial for fetal lung development and maturation (reviewed in Strobel *et al*. 2007). Interestingly, liver stores of retinol in human fetuses were found to increase with the progress of gestation and to vary with maternal retinol levels, with the influence of maternal status being greater in later pregnancy than in the earlier stages (Shah & Rajalakshmi 1987). Consequently, supplementation after mid-pregnancy at physiological levels can improve fetal stores without the risk of teratogenic effects. Insufficient vitamin A intake seems to be associated to low birthweight (LBW) (Strobel *et al*. 2007).

Dietary antioxidants (i.e. vitamin C, vitamin E, selenium, zinc, beta-carotene) enhance many aspects of the immune response and limit pathological aspects of the cytokine-mediated response (Bendich 2001; Arrigoni & De Tullio 2002). Recent reports associate poor maternal selenium status as a nutritional factor predisposing mothers to pre-eclampsia, as women who develop pre-eclampsia have a lower selenium

Table 2. The biological role and the reliable biomarkers or indicators of status of micronutrients of considerable public health significance

Micronutrient	Function	Indicators of status	References
Folate	Involvement in the DNA cycle (cell replication); methylation cycle (amino acids cysteine and methionine cycle)	Erythrocyte folate[†]; serum/plasma folate[†]; serum/plasma total homocysteine[†]	WHO/FAO 2004; McNulty & Scott 2008
Vitamin B_{12}	Conversion of homocysteine to methionine as cofactor of the methionine synthase	Serum/plasma vitamin B_{12}[†]; serum/plasma methylmalonic acid (MMA)[†]	Ryan-Harshman & Aldoori 2008; Hoey *et al.* 2009
Vitamin A	Growth and differentiation of a number of cells and tissues	Serum retinol[†]	Ross 2006
Vitamin D	Bone resorption, intestinal calcium transport (calcium and bone homeostasis), modulation of transcription of cell cycle proteins, and cell-differentiating, anti-inflammatory and immunomodulatory properties	Plasma 25-hydroxyvitamin-D [25(OH)D]	WHO/FAO 2004
Iodine	Synthesis of thyroid hormones	Urinary Iodine excretion in 24 h[†]; serum thyroid-stimulating hormone (TSH)[†]	WHO/FAO 2004; Zimmerman 2008; Ristic-Medic *et al.* 2009
Iron	Haematopoiesis; nucleic acid metabolism; carrier of oxygen to the tissues by red blood cell haemoglobin; transport medium for electrons within cells; integrated part of important enzyme systems	Haemoglobin[†]; serum ferritin[†]; serum transferrin receptor[†]	WHO/FAO 2004; Wood & Ronnenberg, 2006; Zimmerman 2008
Zinc	Structural, regulatory and catalytic functions as cofactor for numerous metalloenzymes	Plasma/serum zinc[†]; prevalence of inadequate intakes of dietary zinc[†]	McCall *et al.* 2000; Lowe *et al.* 2009
Selenium	Protection of body tissues against oxidative stress, maintenance of defences against infection, and modulation of growth and development	Plasma/serum selenium[†]; platelet or erythrocyte selenium[†]; selenium-related proteins[†]	WHO/FAO 2004; Sunde *et al.* 2008

Indicators of status were taken from a table compiled by the Biomarkers of Status Working Party, which comprised a group of international micronutrient experts and EURRECA partners (Fairweather-Tait 2008), and successive updates[†]. Biomarkers reported here are those rated Excellent or Good according to a star rating used to classify the range of biomarkers available for each mineral/vitamin in relation to the limitations of the method.

[†] Also reviewed in 'Biomarkers of status/exposure. Minerals and vitamins'. RA1.2 Status Methods/IA3 Individuality, Vulnerability and Variabilit. July, 2008; 'BIOMARKERS OF STATUS/EXPOSURE. Iron, Zinc, Vitamin A, Vitamin B12, Folate, Iodine & Selenium'. RA1.2 Status Methods/IA3 Individuality, Vulnerability and Variability. February, 2010 (http://www.eurreca.org).

status (Rayman *et al.* 2003). Through the selenoproteins, selenium plays a critical role in regulating the antioxidant status. The various demands of pregnancy impose oxidative, metabolic and inflammatory stresses on the mother (Redman *et al.* 1999). When occurring during embryogenesis and in the placenta, oxidative stress causes adverse pregnancy outcomes such as birth defects, early pregnancy failure, miscarriage and pre-eclampsia (Agarwal *et al.* 2005; Jauniaux *et al.* 2006; Forges *et al.* 2007). Oxidative stress and inflammatory mediators seem to be involved in the abnormal implantation associated with pre-eclampsia (Roberts *et al.* 2003; Vanderlelie *et al.* 2005). Dietary antioxidants seem to play a crucial role in regulating the antioxidant status, thereby aiding in maintaining health. As an example, when comparing women with a higher level of prenatal vitamin C ($\geq 11.734\ \mu g\ mL^{-1}$) to women with a lower level of prenatal vitamin C ($<8.997\ \mu g\ mL^{-1}$), a significant lower trophoblast expression for the endothelial scavenger receptor low-density lipoprotein receptor-1 (LOX-1) and the apoptotic index in normal full-term pregnancy was detected in women with a higher level of prenatal vitamin C (Ahn *et al.* 2007). This seems to indicate that placental oxidative stress and apoptotic activity were associated with the gestational vitamin C status.

Increasing calcium intake can reduce the risk of pregnancy-induced hypertensive disorders (Thomas & Weisman 2006). A significant association was also observed between low 25-hydroxyvitamin D [25(OH)D] concentrations in early pregnancy and subsequent pre-eclampsia (Bodnar *et al.* 2007). Moreover, a significant association was found between maternal plasma 25(OH)D concentrations in mid-gestation and the risk of developing gestational diabetes mellitus (Clifton-Bligh *et al.* 2008; Maghbooli *et al.* 2008). Adequate maternal calcium intake can affect positively both maternal and fetal bone health because the fetus is dependent on maternal sources for the total calcium load. On the contrary, maternal bone loss during pregnancy might lead to osteoporosis and fracture either contemporaneously or by reducing peak bone mass in later life (Prentice 1994). It was shown that whole body bone mineral content of fetus increases between 32 and 33 and 40–41 weeks of gestation. Several findings suggest that the greatest fetal calcium accumulation occurs during the third trimester. Hence, calcium consumption should be encouraged during pregnancy to replace maternal skeletal calcium stores that are depleted during this period (Thomas & Weisman 2006). Similarly, 25 mg day^{-1} of vitamin D should be given during the last 3 months of pregnancy or 2500 mg day^{-1} in one dose at the beginning of the last trimester in countries where sunshine exposure is negligible (i.e. in northern countries) or to women avoiding dairy products for [16] cultural or dietary reasons (Salle *et al.* 2000).

The role of iron supplementation during pregnancy is more controversial. An adequate iron intake is mandatory for normal fetal growth and development, although evidence for either a beneficial or harmful effect of iron prophylaxis on pregnancy outcomes is inconclusive and routine supplementation in pregnancy is a matter of debate (Breymann 2002). Iron-deficiency anaemia (IDA), early in pregnancy, has been found to be inversely related to placental size and associated with reduced infant growth and increased risk of adverse pregnancy outcomes (Scholl & Hediger 1994; Hindmarsh *et al.* 2000; Ronnenberg [17] *et al.* 2004; Buckley *et al.* 2005). Moreover, maternal anaemia during the second trimester has been associated with an increased risk of preterm delivery (Scholl 2005). New insights are emerging into the role of iron on neurocognitive and neurobehavioural development of the fetus during the last two-thirds of gestation and into the long-term consequences of [18] their perinatal deficiency (Beard 2003; Beard 2008). Human brain growth spurt begins in the latter part of the second trimester (Lukas & Campbell 2000), but its peak velocity is during the last trimester of gestation and the first post-natal months (reviewed in Innis 2003). As the physiological needs of some women for iron are not achieved during the last two-thirds of pregnancy with food only, supplemental iron is therefore needed (Beaton 2000). Pregnant women using iron supplements have a better iron status and a lower frequency of IDA compared with women receiving no supplement (Makrides *et al.* 2003; Milman *et al.* 2005). Hence, pre-partum IDA seems to be prevented by oral iron supplements (30–40 mg day^{-1}) taken from the 20th week of gestation until delivery (Milman *et al.* 2005). Women supplemented with iron presented a higher mean birth weight and a lower preterm delivery incidence compared with the control group (Cogswell *et al.* 2003; Siega-Riz *et al.* 2006). On [19] the contrary, high dose of iron supplement (more than 100 mg day^{-1}) was observed to be significantly associated to gestational diabetes (Bo *et al.* 2009).

Iodine intake is required to prevent the onset of subclinical hypothyroidism of mother and fetus during pregnancy, thus to prevent the possible risk of brain damage of the fetus (WHO/FAO 2004). Maternal iodine deficiency leads to fetal hypothyroidism results in cretinism as thyroid hormones are critical for normal brain development and maturation (WHO/FAO 2004). However, if hypothyroidism develops late in pregnancy, the neurological damage is not as severe as when it is already present in early pregnancy (WHO/FAO 2004). Third trimester pregnant women with urinary iodine concentrations below 50 mcg L^{-1} are significantly more likely to have a small-for-gestational-age (SGA) infant. Higher levels of thyroid-stimulating hormone were also associated with a higher risk of having an SGA or LBW newborn (Alvarez-Pedrerol *et al.* 2009). A randomized trial showed that a daily dose of 200 μg iodine starting from 16–20th week of gestation in marginal iodine deficiency appeared to be effective in preventing gestational goiter without enhancing the frequency of post-partum thyroiditis (Antonangeli *et al.* 2002).

Docosahexaenoic acid (DHA; n-3) and arachidonic acid are essential for fetal and neonatal growth and development (Eilander *et al.* 2007), as long-chain polyunsaturated fatty acids are involved in modifications of neuronal membrane fluidity, function of neuronal membrane ionic channels and production of neurotransmitters and brain peptides (Innis 2007). If maternal DHA supply is limited, the fetus is particularly vulnerable to developmental deficits in the third trimester. Adequate maternal DHA intake or supplementation from the second trimester seems to be crucial in avoiding the potential perturbation of cellular environments in the offspring (reviewed in Innis 2003). The PeriLip Steering Committee and the Project Coordinating Committee of the early Nutrition Programming project stated that pregnant women should aim to achieve an average dietary intake of at least 200 mg DHA day^{-1}, and women of childbearing age should be recommended to consume one or two portions of sea fish per week, including oily fish such as salmon, herrings, etc. (Koletzko *et al.* 2008). Beneficial effects on subsequent infant visual function and neurodevelopment were also reported (reviewed in Judge *et al.* 2007 and Innis & Friesen [20] 2008). Potential benefit of enhanced supply of n-3 fatty acids in preventing pre-eclampsia has been suggested in a recent prospective cohort study (Oken *et al.* 2007). Moreover, associations between maternal long-chain polyunsaturated fatty acids supplementation and a small reduction of risk of early preterm delivery in women with high-risk pregnancies (Horvath *et al.* 2007) as well as small increment in the duration of pregnancy (Szajewska *et al.* 2006) have been observed in several studies.

Effect of prenatal micronutrients on lactation and post-natal outcomes

The timing of prenatal micronutrient status and intake has been observed to condition breast milk composition. In particular, maternal vitamin A status from the second trimester of gestation seems to influence both retinol (vitamin A) concentration in breast [21] milk (Mulismatun *et al.* 2001) and newborn development, and inadequacies during pregnancy are not compensated by post-natal supplementation (Strobel *et al.* 2007). Similarly, levels of vitamin E in transitional milk seem to be dependent on vitamin E and polyunsaturated fatty acids intakes during the third trimester (Ortega *et al.* 1999). [22]

The timing of prenatal nutrition seems to impact differently on the nature of adult diseases by programming post-natal pathophysiology. Accumulating data suggest that the early environment may modify the effects of the genome (Newnham *et al.* 2002; Fleming *et al.* 2004; Buckley *et al.* 2005; De Bo & Harding 2006; Gluckman *et al.* 2008). Molecular, cel- [23] lular, metabolic, neuroendocrine and physiological adaptations in the early nutritional environment may cause a permanent alteration of the developmental pattern of cellular proliferation and differentiation in tissue and organ systems that may result in pathological consequences in adult life (Koletzko *et al.* 1998; McMillen & Robinson 2005). Studies in the offspring of women exposed to the Dutch Winter Famine showed that the nutrient challenge in the first trimester of pregnancy was linked to increased prevalence of coronary heart disease and obesity, and to raised blood lipids (Ravelli *et al.* 1999; Roseboom *et al.* 2000; Roseboom *et al.* 2001), whereas famine occurring during late gestation led to decreased glucose tolerance in adult life (Ravelli *et al.* 1998).

Poor maternal vitamin D status early in pregnancy may result in impaired maternal–fetal transfer of 25(OH)D and consequently reduced bone mineral content during infancy and childhood (Javaid *et al.* 2006). There are also arguments that low maternal vitamin D intake from the second trimester of pregnancy may be associated with the risk of recurrent wheeze at 3 or 5 years, suggesting that childhood asthma may be influenced by maternal diet during pregnancy (Camargo *et al.* 2007; Devereux *et al.* 2007). Maternal IDA during the last two-thirds of gestation is suggested to result in irreversible effects on neurochemistry and neurobiology (Beard 2003) such as schizophrenia in later life (Brown & Susser 2008; Insel *et al.* 2008). Data collected from a population-based cohort born from 1959 to 1967, and followed up for development of schizophrenia spectrum disorders from 1981 through to 1997, suggested that second and third trimester exposure to maternal haemoglobin concentrations $\leq$10.0 g dL^{-1} was associated with a fourfold significantly increased rate of schizophrenia disorders in adult offspring (Insel *et al.*

2008). Similarly, in a cohort of births from 1978 to 1998, and followed from their 10th birthday, cohort members whose mothers were diagnosed with anaemia during pregnancy had a 1.60-fold increased risk of schizophrenia (Sørensen *et al.* 2010). It may be proposed that low haemoglobin concentrations compromise oxygen delivery to the developing fetus. In addition, insufficient iron *in utero* exposure may crucially disrupt neurodevelopment given that iron is essential for several metabolic processes involved in the development of brain structures and functions (i.e. dopaminergic neurotransmission, myelination and energy metabolism).

Birth spacing

It has been suggested that short birth intervals, by giving the mother insufficient time to recover from the nutritional burden of pregnancy, could adversely affect the nutritional status of both mother and child (King 2003). This nutritional burden may increase significantly when pregnancy overlaps with lactation, a period of very high maternal nutritional demand (Adair 1993). In a recent systematic review, Dewey & Cohen (2007) reported that, in studies conducted in developing countries, longer birth interval has been associated with a lower risk of child malnutrition in some populations. Where such a significant relationship was shown, the reduction in stunting associated with a pervious birth interval of 35 months ranged from ~10–50%, although considerable residual confounding variables existed in the studies. One study suggested a possible increased risk of maternal anaemia associated with short interpregnancy interval (Conde-Agudelo & Belizán 2000), but iron supplementation during pregnancy was not accounted for in the analysis. There was no clear evidence of a link between interpregnancy interval and maternal anthropometric status, perhaps due in part to changes in hormonal regulation of nutrient partitioning between the malnourished mother and the fetus (Dewey & Cohen 2007). Considering the methodological limitations apparent in the majority of current studies on birth interval and maternal and child nutritional status, there is a clear and urgent need for further research.

Maternal diet

Eating patterns

Eating habits (e.g. vegetarian diet, fast food frequency, breakfast skipping) impact the adequacy of nutrient intakes. Some studies showed an association between dietary patterns and pregnancy outcomes. A reduction in the risk of early delivery has been associated with a maternal mid-pregnancy Mediterranean-type diet rich in fruit and vegetables, that is characterized by high vitamin C, folate, α-tocopherol, magnesium, calcium, iron and vitamin D intake and low sugar and cholesterol intake (Mikkelsen *et al.* 2008). Vujkovic and colleagues (2007) found an increased risk of cleft lip or palate and high plasma total homocysteine levels with a maternal periconceptional Western diet that was high in meat, pizza, legumes and potatoes, and low in fruits.

Vegans may be at risk of vitamin B_{12} deficiency as they do not consume any animal products (ADA Report 2009). A long-term ovo-lacto vegetarian diet has been shown to result in significantly lower serum vitamin B_{12} and higher plasma total homocysteine concentrations during pregnancy and in an increased risk of vitamin B_{12} deficiency with respect to a Western diet (Koebnick *et al.* 2004).

Similarly, meal patterns seem to be related to pregnancy outcomes. It is recommended that pregnant women 'eat small to moderate-sized meals at regular intervals, and eat nutritious snacks' in order to meet the increased nutritional needs. Prolonged periods of time without food can cause hypoglycemia, thus a physiological stress. In a prospective cohort study of risk factors for preterm birth, women were asked to indicate how many meals and snacks they usually ate per day and the time of consumption (Siega-Riz *et al.* 2001). Results showed that consuming food at a lower optimal frequency was associated to a slightly increased risk for delivering preterm mainly after premature rupture of the membranes.

Consumption behaviour in pregnancy is influenced by a complex range of psychological, sociodemographic and cultural factors. For any given community, an understanding of these variables is required when transferring recommendations into action. Social class may affect the quality of diet. On the whole, low-income groups consume a poor-quality diet, and diet-related diseases, such as obesity and diabetes, have begun increasing among lower- and middle-income groups (Popkin 2003). High palatability, high convenience, and the low cost of energy-dense foods in conjunction with large portions and low satiating power may be the principal reasons for overeating and weight gain (Drewnowski & Darmon 2005). In particular, a review undertaken by Darmon & Drewnowski (2008) about the relationship between socio-economic status and eating behaviour showed that studies on the plasma biomarkers of dietary exposure provide evidence that socio-economic status affects vitamin intakes, and that low-income pregnant or breastfeeding women are at greater risk of insufficient vitamin and mineral intakes. For instance, a dietary survey undertaken in UK showed that diet of low-income pregnant women did not meet the EAR for folate, calcium and iron (Mouratidou *et al*. 2006). In addition, maternal education seems to correlate to food choices. As demonstrated in a large population-based birth cohort study in Finland, pregnant women with higher education levels had higher daily consumption of vegetables, fruits and berries, leading to higher intakes of dietary fibres, and of some vitamins (Arkkola *et al*. 2006). Similarly, the Pregnancy, Infection and Nutrition Study in North Carolina, involving 2063 pregnant women, showed that high school graduates had significantly higher Diet Quality Index for Pregnancy scores, and that higher percentages of recommended vegetable servings were consumed by better-educated women (Bodnar & Siega-Riz 2002).

Geographic factors

The micronutrient status of an entire community may be influenced by region and seasonal variation impacting the availability of micronutrients. Iodine and selenium deficiencies tend to be geographically specific because of deficiencies in the soil and therefore the food chain (Ladipo 2000; WHO/FAO 2004). The majority of vitamin D comes from sunlight exposure. In most situations, during summer, approximately 30 min of skin exposure to sunlight in the middle of the day can provide 50 000 IU (1.25 mg) of vitamin D to people with white skin. Latitude and season as well as skin pigmentation and ethnicity influence the ability of the skin to provide the total vitamin D needs of the individual (WHO/FAO 2004; Yu *et al*. 2009). This means that in locations around the equator, the most physiologically relevant and efficient way of acquiring vitamin D is to synthesize it endogenously in the skin (Hollis & Wagner 2004), whereas during winter at latitudes higher than 42°, vitamin D synthesis is virtually zero (WHO/FAO 2004). Taken together, these findings suggest that not routinely sun-replete individuals or persons with darker pigmentation should correct their vitamin D status by consuming the amounts of vitamin D appropriate for their population. Unfortunately, a recent review by Hollis & Wagner (2004) indicated that, currently, the appropriate dose of vitamin D during pregnancy is unknown, although it appears to be greater than the current dietary reference intake of 5–10 μg day^{-1}, and that further studies are necessary to determine optimal vitamin D intakes for pregnancy as a function of latitude and race. This concern was confirmed by a prospective randomized controlled study that took place in the UK comparing the effects of a single dose of 200 000 IU vitamin D (calciferol) and of a daily dose of 800 IU vitamin D (ergocalciferol) from the 27th week to delivery on pregnant women and their baby at delivery (Yu *et al*. 2009). Results showed that despite supplementation enhanced significantly the 25(OH)D levels within supplemented groups with respect to the untreated group, vitamin D sufficiency >50 nmol L^{-1} was achieved only in 30% of supplemented women, and only 8% of babies were vitamin D sufficient in the supplement group.

Micronutrient bioavailability and diet

Appropriate intake of micronutrients depends not only on the quality of diet but also on their bioavailability. Lack of accurate data on micronutrients' bioavailability from natural food sources may be an ongoing concern for policy-makers for setting dietary recommendations. As an example, the recommended nutrient intakes for dietary zinc (mg day^{-1}) to meet the normative storage requirements from diets by the

Table 3. Recommended nutrient intakes for dietary zinc (mg day^{-1}) in pregnancy to meet the normative storage requirements from diets differing in zinc bioavailability and principal dietary characteristics for categorizing diets according to the potential bioavailability of their zinc[†] (adapted from WHO/FAO 2004)

Trimester	High bioavailability	Moderate bioavailability	Low bioavailability
	Refined diets low in cereal fibre and phytic acid content, with phytate–zinc molar ratio <5; adequate protein content principally from non-vegetable sources, such as meats and fish.	Mixed diets containing animal-fish protein. Lacto-ovo, ovo-vegetarian, or vegan diets not based primarily on unrefined cereal grains or high-extraction-rate flours. Phytate–zinc molar ratio of total diet = 5–15, or not >10 if more than 50% of the energy intake is accounted for by unfermented, unrefined cereal grains and flours and the diet is fortified with inorganic calcium salts. Availability of zinc improves when the diet includes animal protein or milks, or other protein sources or milks.	Diets high in unrefined, unfermented and ungerminated cereal grain, especially when fortified with inorganic calcium salts and intake of animal protein is negligible. Phytate–zinc molar ratio of total diet >15. High-phytate, soya–protein products as the primary protein source. Diets in which approximately 50% of the energy intake is accounted for by the following high-phytate foods: high-extraction-rate (≥90%) wheat, rice, maize, grains and flours, oatmeal and millet; chapatti flours and tanok; sorghum, cowpeas, pigeon peas, grams, kidney beans, black-eyed beans and groundnut flours. High intakes of inorganic calcium salts, either as supplements or as adventitious contaminants, potentiate the inhibitory effects, and low intakes of animal protein exacerbate these effects.
First	3.4	5.5	11.0
Second	4.2	7.0	14.0
Third	6.0	10.0	20.0

[†] At intakes adequate to meet the average normative requirements for absorbed zinc, the three availability levels correspond to 50%, 30% and 15% absorption.

Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Consultation on Human Vitamin and Mineral Requirements (WHO/FAO 2004) are stated according to different bioavailabilities (Table 3).

Dietary factors such as food matrix, chemical form, processing and cooking methods may modify micronutrient bioavailability (Hotz & Gibson 2007). They may limit absorption through nutritional interactions (e.g. fibre/phytate–minerals complexes), mineral–mineral interactions involved in the same metabolism, competition for a common transport site or transport ligand (e.g. zinc/copper, iron/manganese), and effects of drugs or chemicals on the metabolism of the nutrient (Keen *et al*. 2003). Alternatively, they may enhance absorption as in the case of iron if the diet contains abundant amounts of vitamin C and meat/fish (Gibson *et al*. 2006), or for carotenoids in the presence of dietary fats (van Het Hof *et al*. 2000), or for zinc by germination of cereals and legumes (Gibson *et al*. 2006). Interestingly, based on this assumption, the footnote to the original table in the Nordic Country recommendation (NNR 2004) (see Table 1) states: 'The composition of the meal influences the utilization of dietary iron. The availability increases if the diet contains abundant amounts of vitamin C and meat or fish daily, while it is decreased at simultaneous intake of, e.g. polyphenols or phytic acid; the utilization of zinc is negatively influenced by phytic acid and positively by animal protein. The recommended intakes are valid for a mixed animal/vegetable diet. For vegetarian cereal based diets, a 25–30% higher intake is recommended'.

Similarly, the form of micronutrient influences its bioavailability: i.e. haem- iron is absorbed better than non-haem iron. On the contrary, there is conflicting evidence as to whether the extent of conjugation of polyglutamyl folate is a limiting factor in folate bioavailability. Estimates of the extent of lower bioavailability of food folates compared with folic acid show great variation, depending on the methodological approach used (McNulty & Pentieva 2006). The EAR for vitamin A, expressed as mg retinol equivalents (mg RE), should account for the proportionate bioavailability of preformed vitamin A (about 90%) and provitamin A carotenoids from a diet that contains sufficient fat (WHO/FAO 2004).

Maternal age

Maternal age represents a critical factor in micronutrient requirement. Accordingly, the dietary recommended intake for micronutrients should take into account maternal age; e.g. US recommendations for vitamin K, vitamin C, calcium, phosphorus, magnesium and zinc in pregnancy are separated for age >18 or ≤18 years by the Institute of Medicine's Food and [26] Nutrition Board (http://www.usda.gov). Adolescent pregnancy, as defined by WHO as pregnancy in those [27] aged 10–19 years (WHO 2004), appears to be a risk factor for micronutrient deficiencies (Lenders *et al.* [28] 2000; Hall Moran 2007a). A systematic review of the nutrient intakes of pregnant adolescents living in industrialized countries suggested that, compared with US dietary reference intake values, intake of energy, iron, folate, calcium, vitamin E and magnesium were lower than those currently recommended (Hall Moran 2007b).

In recent decades, adolescent pregnancy has become an important public health issue because of associated poor obstetric outcomes, particularly with respect to fetal growth restriction and preterm delivery. Approximately a fifth of all births worldwide are to adolescent mothers (Population Reference Bureau 2000) and, although the general trend over the past 20 years in Europe is that of declining adolescent pregnancy and birth rate, the distributions across Europe are large, ranging from 42.69 live births per 1000 women aged 15–19 in Tajikistan to 5.39 live births per 1000 women in Switzerland (Avery & Lazdane 2008). Despite this, relatively little is known about nutrient intakes of adolescents during pregnancy, and few prospective studies have been conducted in this population. One recent prospective, observational study of 500 adolescents conducted in the UK highlighted the extent of poor vitamin D status in pregnant adolescents and suggested a clear relationship between maternal folate and iron status and the incidence of SGA birth and preterm delivery in this cohort (Baker *et al.* 2009).

Despite the increasing prevalence of pregnancy in women over the age of 40 years as a result of recent advances in assisted reproductive technology, to our knowledge, there are no studies related to nutritional needs and reference values in this population of pregnant women. This lack of knowledge is reflected in the European micronutrient recommendations for pregnancy, the vast majority of which do not differentiate for maternal age.

Conclusion

Targeted recommendations must be given to guide pregnant women in their food choice and dietary supplement use so that they may obtain adequate nutritional status and meet the increased need for nutrients. The term 'vulnerability' represents a key concept in assessing nutrient needs and defining recommended nutrient intakes for target populations at risk of low intake. Several physiological and metabolic factors characterize pregnant women such as adaptation and timing of gestation, and determine their nutritional requirements. In addition, environmental and demographic variables seem to influence the overall quality of diet and the adequacy of micronutrient intake during pregnancy. Unfortunately, a large number of European recommendations do not consider these factors. Moreover, current research is limited by sampling and measurement bias, and findings are often inconclusive or contradictory. Thereby, further studies and actions are urgently warranted to address limitations and to:

- determine optimal biomarkers and concentrations even with regards to non-classic actions of micronutrients on maternal and fetal outcomes;
- investigate of the most effective way to supply micronutrients, including appropriate timing and dosage. In this context, strategies of supplementation and dietary intervention are currently under discussion. Several studies are ongoing to evaluate the effect of different timing in pregnancy (i.e. early or late pregnancy) as well as the different frequencies of supplementation (i.e. daily or weekly). Forms of micronutrient supplement/intake are also of interest as it is well acknowledged that micronutrient status is

influenced by both the content and the bioavailability of the micronutrient in the diet;

- explore the influence of age and of role of socio-economic factors on the nutrient requirements of pregnant women.

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