Abstract

Pregnancy represents a period of crucial changes in the maternal organism and metabolism, aiming to ensure proper fetal growth and development, as well as maternal preservation. This review focuses on maternal nutrition, and particularly on micronutrient deficiencies and supplementation during pregnancy. Nutrient deficiencies and consequences in pregnant women are presented, with an overview of current recommendations for dietary supplementation in pregnancy, even considering the risk of micronutrient overload. Appropriate universal supplementation and prophylaxis/treatment of nutritional needs currently appears to be the most cost-effective goal in low-income countries, thus ensuring adequate intake of key elements including folate, iron, calcium, vitamin D and A. In high-income countries, a proper nutritional assessment and counselling should be mandatory in obstetric care in order to normalize pregestational body mass index, choose a healthy dietary pattern and evaluate the risk of deficiencies.

Introduction

Pregnancy represents a period of crucial changes in the maternal organism and metabolism, in order to ensure proper fetal growth and development, as well as maternal preservation and survival [1]. Adequate pregestational nutritional status, as well as proper gestational weight gain and dietary intakes are mandatory to promote these processes and to avoid potentially adverse maternal and pregnancy outcomes [2 - 7]. Therefore, it is important to evaluate, monitor, and if appropriate, make changes to improve maternal nutritional status both before and during pregnancy. Moreover, inadequate and excessive dietary intakes have been associated with long-term effects and non-communicable diseases in the offspring (developmental model for the origins of disease, Barker Hypothesis). Particularly, fetal development in obesogenic intrauterine environments can permanently modify individual biological and metabolic pathways, leading to adaptive pathophysiological alterations in the offspring and to increased risks of non-communicable diseases in adulthood [8]. This gives a critical role to preconception and pregnancy care in order to improve health of future generations and prevent transmission of obesity and non-communicable diseases in the offspring.

Micronutrient supply in pregnancy: is diet enough?

Despite a small change in caloric and macronutrient requirements compared to the non-pregnant state, the need for micronutrient supply exponentially increases during pregnancy, particularly for key elements including iron, folate, iodine, calcium and vitamin D [1]. Together with a limited availability of nutrients and fortified foods in low-income countries and with an alarming decline of appropriate nutritional habits in high-income countries, this explains

why micronutrient deficiencies are extremely common during pregnancy [9]. This raises the question whether dietary intake is enough to cover the increased micronutrient requirements of pregnancy. The World Health Organization (WHO) currently recommends to provide multiple micronutrient supplements to pregnant women from populations with a high prevalence of maternal nutritional deficiencies, thus reducing the risks of low birthweight (LBW) and small-for-gestational-age (SGA) compared to iron-folic acid supplementation alone [10, 11]. Conversely, discordant results question the efficacy of routine multivitamin supplementation among well-nourished women from high-income countries [12]. Despite high food availability, several issues need to be pointed out. Firstly, a general switch to a high fat, low quality-diet has been detected in recent decades in high income-countries, leading to a huge increase in obesity rates and micronutrient deficiencies [6]. Secondly, even nutrient-dense food choices may not meet nutrient goals, not only due to the increased requirements of pregnancy, but also to a general reduction of food quality and nutritional value [13, 14]. Finally, previous studies showed that pregnant women do not consistently change dietary habits compared to the pregestational period, further increasing the possibility of mismatch with the increased demands of the feto-placental unit [15]. This was confirmed by a number of observational studies, showing dietary micronutrient intake consistently below the recommended for pregnant women in high-income countries [16, 17]. To address this gap, supplementation during pregnancy has become increasingly popular, with a prevalence of use ranging from 70 to 97% in developed countries [16, 18]. A Norwegian study on 40,108 women showed that the nutrient contribution of dietary supplements among users varied from 65% for folate and vitamin D to 1% for potassium, with total intakes

of vitamin D, folate, iodine and iron still lower than the national recommendations for pregnant women [16]. A recent meta-analysis also provided evidences that fetal gender, pregestational maternal nutritional status and adherence to supplementation represent important factors influencing the effect of multivitamin supplementation on pregnancy outcomes, showing improved survival and outcomes in case of female newborn and undernourished/anaemic pregnant women [19].

Micronutrient intake, supplementation and pregnancy outcomes

Micronutrient intake is known to affect all stages of female reproductive period. Starting as early as the periconceptional period, embryonic morphological development has been definitely associated with maternal folic acid intake and one-carbon metabolism [20, 21], leading to the strong recommendation of the WHO to supplement all women of childbearing potential with daily folic acid 400 µg [22]. Furthermore reproductive performance and consequent impaired fertility have been associated with nutrition, with adherence to healthy dietary patterns and intake of folic acid and omega-3 fatty acids found to be related to better fertility and higher live birth rates in ART procedures [23]. Nutrition has been additionally associated with fetal growth, preterm delivery and maternal hypertensive disorders through the modulation of placental function and inflammatory pathways [24 - 27]. Finally maternal nutrition in the postpartum period has been related to neonatal growth and maternal health and lactation [28, 29]. Figure 1 shows the WHO recommendations for dietary supplementation in pregnant women (insert Figure 1).

Iron

Iron requirements more than double during pregnancy compared to the pregestational period due to feto-placental demands and maternal red blood cell expansion. This leads to an increase in iron need to about 30 mg/day during pregnancy, whereas the requirement for absorbed iron steadily increases from approximately 0.8 mg/day in the first trimester, to 4-5 mg/day in the second trimester, and >6 mg/day in the third trimester [30].

Inadequacies in maternal iron stores primarily result in iron deficiency anemia (IDA, hemoglobin concentrations below 110 g/L in the first and third trimesters or 105 g/L in the second trimester), which affects about 45 million pregnant women worldwide [31, 32]. IDA is further associated with lower gestational age at birth and preterm delivery, LBW, stillbirth and reduced iron stores in the newborn [33]. Since iron dietary intake alone cannot realistically meet the increased demands of pregnancy due to low bioavailability, supplementation is recommended to all pregnant women with a dosage depending on local prevalence of maternal anemia (International Nutritional Anemia Consultative Group). Therefore, in most developed countries, which have a 40% prevalence of anemia in pregnancy, oral ferrous iron 60 mg/day is recommended to all women throughout pregnancy (International Nutritional Anemia Consultative Group). Preventive iron supplementation is associated with a reduction of maternal anemia at term by 70%, while the effects on pregnancy and perinatal outcomes are inconsistent and still controversial, particularly among non-anemic women [34, 35]. As supplementation has been additionally associated with an increased risk of hemoglobin concentrations at term higher than 130 g/l and iron overload is associated with side effects and adverse pregnancy outcomes (i.e. LBW, maternal hypertensive disorders), a supplementation

tailored according to the periconceptional iron status (serum ferritin) represent a reasonable alternative, and excludes about 15-20% of iron-repleted women from the need of supplementation in high-income countries [36] (insert Table 1).

Folic acid

Daily supplementation of folic acid 400-800 µg is recommended for all women of childbearing potential in order to reduce the risk of neural tube defects (NTD) in the offspring, starting from two months before to three months after conception [22]. An increased dosage (4-5 mg/d) is required in case of high risk of NTD or folate deficiency (i.e. previous child with an NTD, use of anticonvulsants, pregestational diabetes), whereas supplement continuation is additionally recommended in association with iron throughrout pregnancy for anemia prevention [37]. Figure 2 shows the available strategies carried out in order to improve folate status among childbearing women worldwide [37] (insert Figure 2). True folate deficiency is rare in countries adopting a policy of food fortification. However, suboptimal levels for NTD prevention (defined by the WHO and the Center for Disease Control as red cell folate <400 ng/mL or 906 nmol/L) are common even in these countries, occurring in about 23% of fertile women [38]. Conversely, the average dietary folate intake of European women, where fortification programs are not implemented, is around 200 µg per day, definitely below the recommended, with further inadequacies in dietary B vitamins and lifestyle (i.e. smoking, alcohol and coffee consumption) leading to an average increase in plasma homocysteine concentrations by 1-4 µmol/l [39, 40]. Given this, routine empiric folic acid supplementation is recommended for all women. The body of evidence from randomized trials supports the efficacy of

folic acid supplementation and dietary fortification for decreasing the occurrence and recurrence of NTDs by about 70%, without clear effects on other birth defects [41]. A recent meta-analysis supports that maternal use of folic acid supplements during pregnancy reduces the risk of autism spectrum disorders in children by 33% [42], while systematic reviews linked folic acid supplementation to a decreased risk of SGA infants [43]. Moreover, as a methyl donor, folic acid has the potential to epigenetically modify gene expression, explaining why intake and supplementation have been associated with DNA methylation in genes related to metabolism, growth, appetite regulation, possibily explaining associations with non-communicable disease in later life [44]. A new body of evidence has recently associated maternal folate intake and status with first trimester embryonic growth, meaning that also embryonic size, previously conceived as independent of environmental factors and constant in all women and pregnancies, can be impacted and modified by maternal nutrition, with long-term effects on birth outcomes and future health [45, 46].

Calcium

The recommended dietary allowance (RDA) for elemental calcium in pregnant and lactating women is 1000 mg/day, unchanged compared to the non-pregnant state and depending on maternal age [47]. Calcium intake among pregnant women often does not meet the recommendation even in developed countries, with estimates of low calcium intake affecting 24% in the United States and more than 30% in some north-European populations [48]. Calcium intake is essential for fetal skeletal development, primarily in the third trimester. Moreover, supplementation is a promising intervention for the prevention of pre-

eclampsia in case of low baseline dietary calcium intake and high risk of hypertensive disorders. This led to the WHO recommendation to supplement pregnant women at risk with 1.5-2.0 g/day of elemental calcium starting from 20 weeks of gestation onwards (2013). A recent systematic review and network-meta-analysis on 28,000 women confirmed that calcium, vitamin D, and calcium plus vitamin D lower the risk of preeclampsia by 46%, 53% and 50% respectively [49]. Calcium supplementation does not reduce this risk in healthy nulliparous women with adequate calcium intake, whereas still controversial are the results regarding the risk of preterm birth and LBW [50].

Iodine

Iodine deficiency is associated with potentially harmful effects in pregnancy, including maternal and fetal/neonatal hypothyroidism, as well as intellectual disability and long-term effects on neurognitive development in the offspring [51, 52]. The Institute of Medicine recommends a daily iodine intake of 220 μg during pregnancy and 290 μg during lactation, while the WHO recommends iodine intake of 250 μg for both pregnant and lactating women. Data surveys showed urinary iodine concentrations identifying inadequate status (<150 μg/L) in about 56% of pregnant women in the United States and data are even more alarming in the European population, where only eight out of 21 countries showed an adequate iodine status (38%) [53]. The extensive policy of salt iodization promoted by the WHO and the Iodine Global Network has underpinned remarkable progress in ameliorating iodine deficiency worldwide, especially during the last decade. Pregnant women should be encouraged to use iodized salt (= 95 μg iodine per one-quarter teaspoon) and consume iodine-rich seafood. Iodine supplementation of pregnant women is recommended in

many regions with mild to moderate maternal iodine deficiency, but both long-term benefits and safety of iodine supplementation are unclear and need further investigation [54].

Vitamin D

Vitamin D is a fat-soluble hormone that plays a pivotal role in calcium, magnesium, and phosphate homeostasis and as an antiproliferative and immunomodulatory mediator. It is primarily obtained *via* skin production from sunlight exposure and only one fifth *via* nutritional intake. Risk factors for vitamin D deficiency in pregnancy include maternal low sun exposure, ethnicity, cloathing and obesity. Maternal vitamin D deficiency, despite varying definitions (25-hydroxy-vitamin D ≤30 nmol/l or ≤25 nmol/l), is extremely common in the Mediterranean region, ranging from 41% to 90%, and has been related to preeclampsia, gestational diabetes, disorders in bone formation, higher risk of cesarean section and preterm birth [55]. Conversely, vitamin D supplementation has been associated with reduced risks of pre-eclampsia, LBW, preterm birth, and atopic diseases in childhood, but data on adverse effects are lacking [56]. Routine supplementation in antenatal care still remains a matter of debate, with the British Nutrition Foundation recommending all pregnant women a daily supplementation containing vitamin D 10 μg, the Institute of Medicine (2011) and Endocrine Society recommending a daily vitamin D intake of 600 IU and 1500– 2000 IU respectively. On the other hand, the WHO does not support universal supplementation. High-quality randomised trials are still required to assess the effect of vitamin D supplementation on pregnancy and newborn outcomes.

Selenium

Selenium is a trace element crucial in antioxidative protection, protein synthesis and immunomodulatory and anti-proliferative mechanisms [57 - 61]. During pregnancy, serum concentrations significantly decrease compared to the non-pregnant state so that the RDA for this element increases to 60 µg/day [62, 63]. Dietary selenium intake appears to be at or above the recommendation in the United States, while considerably lower in most parts of Europe (30-40 µg/day), mainly because of European soils providing a poorer source of selenium [64]. Selenium deficiency has been associated with reproductive and pregnancy complications, but results are inconclusive, as well as the capability of supplementation to prevent reproductive and pregnancy disorders. Observational studies reported associations between low selenium serum concentrations, early pregnancy loss and preeclampsia, probably linked to the reduced antioxidant protection of biological membranes and DNA, leading to implantation disorders and placental disfunction, but results are still inconclusive [63]. It was supposed that selenium supplementation either alone or in combination with a general multivitamin supplement might also delay the onset and severity of preeclampsia, ameliorating placental oxidative stress and buying valuable time for fetal development prior to delivery [65 - 68]. Low concentrations of selenium and antioxidative enzymes have been additionally associated with hepatic impairment in patients with intrahepatic cholestasis [69, 70]. Recent epidemiological and intervention studies revealed a surprising association between high serum selenium levels and type 2 diabetes, hyperglycemia and dyslipidemia, probably due to an interaction between selenoproteins and insulin induced signaling pathways related to carbohydrate and lipid metabolism [71].

Magnesium

Magnesium has a crucial role in body temperature regulation, DNA and protein biosynthesis, cardiac, nervous and muscular excitability and vasomotor tone modulation. Magnesium deficiency is extremely rare in healthy individuals eating a varied diet. The most common causes of magnesium deficiency include inadequate dietary intake or gastrointestinal absorption, increased losses through gastrointestinal or renal systems and increased requirement for magnesium, such as in pregnancy. The role of magnesium in pregnancy has been a matter of investigation for a long time. Retrospective data showed that magnesium supplementation during pregnancy was associated with a reduced risk of fetal growth restriction and preeclampsia, while higher first trimester dietary intake was associated with increased birthweight [72, 73]. Several randomised trials have been performed to evaluate the benefits of magnesium supplementation during pregnancy on maternal and infant outcomes, showing no significant effects on perinatal mortality, SGA infants and preeclampsia [74]. An observational study on the role of magnesium and thyroid function in early pregnancy after in-vitro fertilization (IVF) showed that women with successful pregnancies have higher blood levels of magnesium, so that supplementation prior to ART might be considered in order to improve reproductive success [75]. Despite encouraging reports, current evidence is insufficient to recommend the use of magnesium supplementation for routine clinical practice.

Risk of micronutrient overload

Limited data are available on micronutrient overload and toxicity. However, at very high doses, vitamins and minerals can be potentially toxic, thus representing a crucial topic in high-income countries.

Iron

Excessive iron dietary intakes are associated with increased risk of type 2 diabetes through increased oxidative stress associated with increased insulin resistance [76 - 79]. In addition, serum ferritin concentrations have been positively associated with inflammation, hypertension, metabolic syndrome and higher cardiovascular risk profile [80 - 82]. In pregnancy, excessive iron supplements might expose women to increased oxidative stress, lipid peroxidation, and pregnancy-induced hypertensive disorders [83 - 85]. Two recent meta-analysis suggested that high iron status might contribute to increase the risk of gestational diabetes, possibly mediated by iron oxidative stress [86, 87]. The overproduction of reactive oxygen species can represent an important mediator of damage to cell structures, including lipids, proteins and DNA. Furthermore, high iron status could lead to increased platelet aggregation and higher thrombotic risk [88]. It could therefore be hypothesized that iron depletion during pregnancy might represent a physiological condition to prevent the adverse effects of oxidation, insulin resistance, and thrombosis. Gastrointestinal side-effects are commonly reported as adverse effects associated with oral iron treatment and include nausea, flatulence, abdominal pain, diarrhea, constipation, and black or tarry stools [89]. Several studies consistently showed that soluble oral iron negatively impacts the colonic microbiota, promoting the presence of potentially pathogenic bacteria at the expense of beneficial bacteria [90 - 92]. Finally, available iron has been proposed as a risk factor for colon inflammatory signalling and colorectal carcinogenesis through the loss of the key intestinal tumor suppressor Apc [93]. Targeting iron supplementation according to periconceptional iron status

could represent a cost-effective strategy to optimize iron stores and pregnancy outcome, reducing the risk of overload and negative consequencies.

Folic Acid

As folic acid intake may delay the diagnosis of vitamin B12 deficiency, masking megaloblastic anemia and thus allowing progression of neurologic abnormalities, any vitamin B12 deficiency should be ruled out before starting folic acid supplementation [94]. This explains the upper level of folate intake set to 1 mg/day. Taking multivitamins containing both folic acid and vitamin B12 reduces any potential risk. As folic acid plays a role in DNA methylation and epigenetic modulation of gene expression, folic acid supplementation has been controversially associated with long-term adverse childhood effects for the exposed fetus, particularly for atopic and reactive airway diseases, insulin resistence and body mass composition [95, 96]. Moreover, folate, as a crucial cofactor involved in DNA synthesis, is critically required for cell division and growth, thus explaining the use of antifolate drugs in cancer chemotherapy. This raises the question whether folic acid supplementation could eventually lead to increased risks of carcinogenesis. In this regard, a 35-year follow-up study of women receiving 0.2-5 mg folic acid daily during pregnancy showed a subsequent non-significant increase in breast cancer mortality, and several other concerns regard associations between folate status and colorectal carcinogenesis [97]. More definitive evidence of beneficial or harmful effects of folic acid on carcinogenesis are still necessary and many factors, including age, sex, vitamin B12, alcohol, smoking, and polymorphisms in genes coding for enzymes related to the one-carbon metabolism need to be included as confounders [98, 99]. Despite these controversies, at this time, no change in

the recommendations for folic acid supplementation in pregnancy is appropriate.

Iodine

Excessive intake of iodine, reported in Japanese women whose diet contains large amounts of seaweed, can cause fetal goiter, but the safe upper limit of iodine intake in pregnancy is unclear. Fetal hypothyroidism is most commonly caused by iodine deficiency, but it has been reported in women ingesting 2.3 to 12.5 mg of iodine daily [100 - 102].

Vitamin A

In humans, isotretinoin, a synthetic retinoid used in the treatment of severe acne, has been associated with a 25 time higher risk of congenital malformations [103, 104], mainly affecting the development of cephalic neural-crest cells and derivatives and perhaps interfering with the neural tube closure [105 - 108]. Vitamin A may become toxic for the mother and her fetus when levels of intake exceed 10000 IU daily or 25 000 IU weekly [109]. β- carotene, a precursor of vitamin A, may be preferred over vitamin A supplements in pregnant women because excess of β-carotene is not known to cause birth defects. Some foods are fortified with vitamin A and others are rich in vitamin A (eggs, liver). For this reason, some groups (e.g. Finnish Food Safety Authority, National Health Service) recommend to limit the intake of liver and liver products mainly in the first trimester of pregnancy, particularly in high-income countries where vitamin A deficiency is rare [110, 111]. The symptoms of acute vitamin A toxicity, generally resulting from excessive supplementation, include dizziness, nausea, vomiting, headaches, blurred vision, vertigo, reduced muscle coordination, skin exfoliation, weight loss and fatigue.

Selenium

Chronic toxicity of selenium in humans results in selenosis, a condition characterized by nervous system abnormalities, cutaneous and hair damage, gastrointestinal syntoms, and rash. This has been reported for selenium intake higher than 850 µg/day. The tolerable upper intake level for selenium has been set at 400 µg/day by the Institute of Medicine [112].

Conclusions

Nutritional counselling should always be included in obstetric care, both in low income and high-income countries, thus improving pregnancy outcome, maternal survival and future health outcome in the offspring. Multivitamin supplementation of all pregnant women represents the most cost-effective goal in low-income countries in order to reduce both maternal and fetal adverse outcomes compared to iron-folic acid supplementation alone. Pregnant women from high-income countries should always receive a proper nutritional assessment and counselling as early as the periconceptional period in order to normalize BMI, choose a healthy dietary pattern (the so called Prudent diet or Mediterranean dietary pattern) and improve pregnancy outcome. Dangerous habits including skipping meals, limiting food or special diets, low frequency of consuming calcium foods, vegetables, or fruits and high intake of sugars/fats need to be investigated. In case of increased risk of micronutrient deficiency, multivitamin supplementation could be a reasonable option to optimize micronutrient intake in pregnancy even in developed countries, with a low risk of micronutrient overload [113, 11, 114]. Proper evaluation of dietary intake and nutritional status (i.e. ferritin level in the periconceptional period) will also consistently reduce the risk of nutrient overload among these women. Table 2 summarizes current policies of micronutrient supplementation and the associated risks of deficiencies and overload (Insert Table 2).

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Figures Legend

Figure 1. Micronutrient deficiencies and WHO recommendations for supplementation in pregnancy.

Figure 2. Worldwide strategies to implement folate status among women of childbearing age [37]**.**

Micronutrients in pregnancy

Deficiencies are different in high and low-income countries, according to geographical area and nutritional habits

SPECIFIC AREAS
vitamin A
iodine
vitamin D
calcium

Supplementation is recommended only in specific areas at high risk for deficiencies. Supplementation policy needs further investigation

WORLDWIDE
iron
folate

Supplementation is strongly recommended worldwide

Worldwide strategies to optimize folate status

1. Increased dietary intake

→ food folate is 1.7 times less bioavailable than synthetic folic acid
→ usual daily intake of folate is about 0.16-0.20 mg/day
→ a 3.5-fold increase in daily folate intake would require unrealistic intake of folate-rich food (i.e. about 15 servings of broccoli each day)

this is not a convincing strategy

2. Mandatory food fortification

→ Leads to an estimated intake of 0.1-0.2 mg/day
→ Currently 53 countries worldwide
→ Passive intervention with low risk of overload, but no assurance that all target groups will receive adequate amounts of the fortificants

3. Supplementation: folic acid/multivitamin supplements (0.4-0.8 mg)

→ risk: unplanned pregnancies

4. Future: the US FDA (Food and Drug Administration) approved a new oral contraceptive comprising levomefolate calcium as the folate component besides contraceptive components

Table 1. Preventive iron supplementation for non-anemic pregnant women according to periconceptional iron status (ferritin concentrations) and treatment recommendations for anemic women [36].

Non-anemic pregnat women		
Serum ferritin (mg/L)	**Supplementation**	**Pregnant women (%)**
> 70-80	No iron supplement	15-20
30-70	30-40 mg/day	40
<30	60-80 mg/day	40
Mild to moderate anemic pregnant women		
Hb<110 g/L	Elemental ferrous iron 100-200 mg/day	

Table 2. Summary of micronutrient supplementation during pregnancy and risks of deficiency and overload.

Micronutrient	Implications for deficiency	Supplementation policy	Risks of overload
Iron	Maternal IDA with increased risks of preterm delivery, LBW, stillbirth and reduced iron stores in the newborn	Universal supplementation according to the prevalence of anemia (60 mg/day for IDA prevalence of 40%) *or* Supplementation tailored to iron stores (see Table 1)	- Gastrointestinal side effects - Increased risk of hemoglobin concentrations at term higher than 130 g/l - Adverse pregnancy outcomes (e.g. LBW, maternal hypertensive disorders, thrombotic risk, gestational diabetes)
Folic acid	- NTD - Increased risks of LBW and non-communicable diseases in adulthood	Universal, 400-800 µg/day starting from two months before to three months after conception *or* 4-5 mg/d in case of high risk of NTD or folate deficiency Supplement continuation is recommended in association with iron throughrout pregnancy for anemia prevention	- Delay in vitamin B12 deficiency diagnosis, masking megaloblastic anemia with neurologic consequences - Colorectal carcinogenesis?
Calcium	- Impaired fetal skeletal development - Increased risk of maternal hypertensive disorders	1.5-2.0 g/day of elemental calcium starting from 20 weeks of gestation onwards in case of risk for deficiency or hypertensive disorders	Maternal side effects (e.g. gastrointestinal)
Iodine	Maternal and fetal/neonatal	Recommended intake of 250	Fetal goiter

	hypothyroidism, intellectual disability and long-term effects on neurognitive development in the offspring	µg/day for pregnant and lactating women	
Vitamin D	- Impaired fetal bone formation - Controversial associations with risks of preeclampsia, LBW, gestational diabetes, cesarean section and preterm birth	Universal supplementation 10 µg/day - 600 IU/day *Or* Women at risk for deficiency	Controversial small increase in kidney stones
Selenium	Controversial associations with early pregnancy loss, preeclampsia, intrahepatic cholestasis	60 µg/day	Selenosis (tolerable upper intake level 400 µg/day)
Magnesium	Controversial associations with fetal growth restriction and preeclampsia	240 mg/day	Not reported
Vitamin A	Maternal anemia, night blindness, congenital malformations	Supplementation is only recommended to prevent night blindness in areas where vitamin A deficiency is a severe public health problem (10000 IU/day, or 25000 IU/week)	- Congenital malformations for intake higher than 10000 IU daily - Maternal side effects

IDA: iron deficiency anemia; LBW: low birth weight; NTD: neural tube defects.