Essentiality of Trace Element Micronutrition in Human Pregnancy: A Systematic Review

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Abstract
The physiological challenges and metabolic demands of pregnancy increase maternal nutritional requirements for macro and micronutrients, critical for the establishment and maintenance of a healthy pregnancy. Trace elements are essential for a variety of cellular processes, and their deficiency has been linked to complications of pregnancy such as preeclampsia, preterm delivery and small for gestational age babies. Growing evidence suggests that populations of both developing and developed nations may be at risk of sub-optimal micronutrient intakes and that micronutrient supplementation may provide a cost-effective and safe strategy to improve pregnancy outcomes. This review evaluates the importance of essential trace element micronutrition in pregnancy and discusses the benefits of supplementation on maternal outcomes and fetal development. The potential importance of key essential trace elements; magnesium, copper, zinc, calcium, iodine, manganese, selenium and iron are discussed and their importance in pregnancy considered.

Keywords: Trace elements; Micronutrition; Supplementation; Pregnancy; Preeclampsia; Preterm labour; Preterm delivery

Abbreviations: RDI: Recommended Daily Intake; UL: Upper Level Intake; SOD: Superoxide Dismutase; WHO: World Health Organisation; UIC: Urinary Iodine Concentration; GPx: Glutathione Peroxidase; ThxRed: Thioredoxin Reductase; Hb: Haemoglobin

Introduction
During pregnancy, progressive physiological changes fundamental to supporting the metabolic demand of the growing fetus increases a woman’s micronutrient requirement [1]. Characteristic elevations in oxygen consumption, central hemodynamic alterations, and oxidative stress, are essential to fetal development and contribute to the long standing recognition of pregnancy as a vulnerable period which is important in determining life-long health. It is important to ensure that women receive adequate macro and micronutrition prior to and throughout pregnancy to optimise their capacity to manage these physiological challenges and ensure the well-being of the growing fetus. Micronutrient deficiencies have been associated with significantly higher reproductive risks both in the conception period and throughout the course of gestation [2-4] and may include anaemia, pregnancy induced hypertension and preeclampsia, fetal growth restriction, labour complications leading to increased maternal and fetal morbidity or mortality [5, 6].

Pregnant women living in developing countries or from low-income areas of developed nations can often be exposed to inadequate macro and micronutrition. Suboptimal consumption results in lower than recommended pregnancy weight gains as a possible result of limited access to and intake of animal products, fruits, vegetables and fortified foods [7]. During pregnancy the increased nutritional demands placed on key maternal physiological systems may exacerbate pre-existing suboptimal micronutrient status and contribute to the increased prevalence of adverse maternal and fetal outcomes in these populations [8].

It is well established that women living in developed countries are on average better nourished in terms of macronutrient intakes due to the relatively ease of access to the appropriate foods. However, excessive intakes of carbohydrates, fats and proteins in these populations has seen an increasing prevalence of health conditions such as obesity, hyperlipidaemia and Type 2 diabetes [9]. Significant evidence suggests that these metabolic conditions increase the incidence of pregnancy complications such as preeclampsia, preterm delivery and gestational diabetes [10-12]. Even in these populations of the developed world which are adequately meeting their macronutrient requirements, it has been suggested that women may also be suffering from micronutrient deficiencies prior to or as a result of the increased demands of pregnancy, as well as the result of maternal genetics, smoking, infection and alterations in nutrient absorption and utilisation [13, 14].

In the developed world there has been a shift towards the utilisation of multivitamin supplements during pregnancy to meet the increased requirements of folate, iron and B group vitamins widely accepted as important for the establishment of a healthy pregnancy. Comprehensive supplementation has been linked with improved pregnancy outcomes [15-17] and these multivitamin preparations may be of value to maternal metabolism by overcoming multiple micronutrient deficiencies [13]. Information regarding the importance of trace element micronutrition in pregnancy is sporadic and varies depending on the availability of population based and supplementation studies. The current paper will focus on the potential importance of eight essential trace elements; magnesium, copper, zinc, calcium, iodine, manganese, selenium and iron, in the course and outcome of pregnancy.

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Methods

The present paper summarises the available data on magnesium, copper, zinc, calcium, iodine, manganese, selenium and iron that are an essential part of micronutrition in human pregnancy. This study utilised a search of electronic databases OVID (MEDLINE), PubMed, and The Cochrane Library for articles published in English without date restriction. The procedure was concluded by the perusal of the reference sections of all relevant articles or reviews, a manual search of key journals and abstracts from the field of pregnancy and nutrition.

Search terms were entered by combining the terms supplement terms including; micronutrient, multivitamin and trace element with pregnancy specific terms such as pregnancy, preterm labour, preterm delivery, preeclampsia and pregnancy complications. Pregnancy specific search terms were also utilised in combination with specific trace element search terms such as copper, calcium, magnesium, zinc, iodine, manganese, selenium and iron.

Following initial identification of all publications related to the search topics above, a careful screening process, following PRISMA Guidelines, was undertaken to eliminate duplicates, limit studies to those conducted in humans and those studies with a clearly defined intervention protocol (Figure 1).

Results for Essential Trace Elements

Magnesium

Humans require relatively large amounts of magnesium in order to activate various essential metabolic enzymes [5] that they obtain from sources such as meat and diary products, bread, cereals, and vegetable. The recommended daily intake (RDI) of magnesium for the general population is 300 to 350 mg/day [18] (Table 1). Magnesium deficiencies are infrequent in individuals with access to a balanced diet though additional magnesium supplementation may be required to meet the demands of pregnancy. It is therefore recommended that a daily intake of up to 400 mg/day of magnesium should be consumed for the duration of pregnancy [18] (Table 1).

Magnesium plays a significant role in blood pressure regulation. Through its effect on calcium channels in vascular smooth muscle, magnesium produces arterial relaxation and the subsequent lowering of peripheral and cerebral vascular resistance, vasospasm, and arterial blood pressure which is of benefit during pregnancy [19]. With such an important role in blood pressure regulation it is not surprising that magnesium deficiency has been linked to preeclampsia [20,21], a hypertensive disorder of pregnancy which may commonly be characterised by significantly lower serum magnesium levels than non-pregnant, healthy individuals [20]. The combination of effects on blood pressure, its capacity to act as a blood brain barrier protectant and anticonvulsant has seen magnesium rise to be one of the most commonly used medications in the treatment of preeclampsia. Since the early 1990s magnesium sulphate has been administered for the control of eclamptic convulsions with an associated reduction of maternal mortality [22] and is considered an essential component of treatment for women with severe preeclampsia.

In the later stage of pregnancy, magnesium has been found to influence the initiation of uterine contractility and therefore onset and progression of labour. Low serum magnesium has been suggested as a marker for patients with a high risk of preterm parturition [19] and supplementation with magnesium for the duration of the pregnancy has been proposed as a possible preventive against preterm delivery [19].

Adequate levels of magnesium can be found in most normal balanced diets, and there are concerns surrounding the safety of magnesium supplementation at doses up to 3 times normal concentrations advocated during eclamptic treatment [23]. In reality, magnesium toxicity is rare when administered using oral supplements due to the fact that 90% of magnesium will be excreted by the kidneys. Careful consideration must be given when administering bolus doses via an IV or IM route to ensure renal function can handle the excretion load to avoid serum magnesium elevations. Adverse maternal effects regarding magnesium toxicity include death from overdose [24], increased bleeding time [25-27], increased blood loss at delivery [28], slowed cervical dilatation and increased pulmonary oedema [29].

Copper

Copper is found in all plant and animal tissues and is important for its biological roles in connective tissue formation, iron metabolism, melatonin production, cardiac function, immune function, and central nervous system development [30]. The essentiality of copper for haematopoiesis makes it especially important during pregnancy considering the significant maternal hemodynamic changes associated with increasing gestation. Copper is also an essential cofactor for antioxidant enzymes, including Copper/Zinc superoxide dismutase (SOD) and cytochrome C oxidase [31]. Both are expressed in maternal and fetal tissues during pregnancy and play an important role in combating the oxidative stress associated with pregnancy. Without this protective mechanism, elevations in oxidative stress may contribute to poor pregnancy outcomes such as preeclampsia, fetal growth restriction and sporadic miscarriage [32].

The RDI of copper for the general population is 1.2 mg/day with an increase to 1.3 mg/day recommended during pregnancy and an UL of 10 mg/day.

Figure 1: Schematic representation of methodology.
intake of 10 mg/day [18] (Table 1). Copper can be found in dietary sources such as shellfish, nuts, seeds, legumes, bran, liver and organ meats and individuals need to ensure they eat a healthy, varied diet to reduce their risk of developing copper deficiency and associated complications. There is currently no reliable biomarker for copper status and as such it is difficult to establish copper levels in individuals or populations. Analysis of dietary copper intakes suggest that females are generally consuming below the recommended levels which may lead to deficiency states when copper requirements increase during pregnancy [33].

**Zinc**

Zinc is essential for multiple aspects of metabolism [34] through its incorporation in antioxidant proteins (Cu/Zn SOD) [35], zinc dependent enzymes, binding factors and transporters that are required for cell replication, division, differentiation, maturation and adhesion [36]. Approximately 95% of the body’s zinc is located within cells and dietary sources of zinc include meat, seafood, legumes and whole-grain cereals [34]. The RDI for zinc is 8 mg/day with an UL intake of 40 mg/day [18] (Table 1).

Zinc plays an important role during pregnancy and lactation, including embryogenesis, fetal growth, development and milk secretion. Depending on zinc bioavailability in the diet, about 2-4mg of additional zinc is required during pregnancy to meet physiological demand [37]. Up to 82% of pregnant women worldwide are considered to have insufficient zinc intakes [38]. It is estimated that maternal zinc requirements during the third trimester of pregnancy increase to approximately double that of non-pregnant women [5] as a result of the progressive decline in the maternal zinc concentration due to haemodilution and the increased transfer to the growing fetus [39]. Zinc deficiencies have been associated with complications of pregnancy and delivery, such as preeclampsia, premature rupture of membranes, preterm delivery, fetal growth retardation and congenital abnormalities [34]. Severe zinc deficiency is rare and isolated to several geographic regions [37] and associated with significant effects on pregnancy outcomes including prolonged labour and fetal growth restriction.

There have been a number of studies examining the effects of zinc supplementation on the duration of pregnancy and incidence of preterm delivery. Supplementation resulted in a lengthened average duration of pregnancy, reduction in the incidence of preterm delivery and increases in the average birth weight of infants that was associated to increased time spent in utero [38]. Zinc supplementation during pregnancy has shown benefits by reducing the incidence of pregnancy induced hypertension, low birth weight infants and preterm delivery [40].

**Calcium**

Calcium is transported across the placenta via an active transport mechanism to help meet the demands of tissue and bone development in the growing fetus. As a result women require an increased intake of calcium during pregnancy [41] in order to maintain maternal calcium balance and bone density. Calcium cannot be manufactured in the body, and daily calcium requirements must be met by the diet with the vast majority supplied by the consumption of dairy products. The RDI of calcium during pregnancy is 1300 mg/day which is a 300 mg/day increase from the RDI for the general population [18] (Table 1). The upper limit of calcium intake is 2500 mg/day.

Despite the fact that adequate calcium requirements can be met through dietary intake, supplementation is recommended during pregnancy as deficiency can be harmful to the long term bone health of the mother and the developing fetus. The impact of calcium supplementation varies according to baseline calcium intake and pre-existing risk factors. Calcium supplementation with at least 1000 mg/day has been associated with the prevention of pregnancy induced hypertension, preeclampsia, preterm birth and lowered the risk of hypertensive complication of pregnancy [42,43].

Calcium has been widely investigated for its relationship to preeclampsia. Several studies have associated a reduction in calcium intake to an increased risk of preeclampsia. Low calcium intakes may precede the development of hypertension by stimulating the release of parathyroid hormone and renin which results in increased intracellular calcium [44] and corresponding increases in vascular resistance and vasoconstriction. Insufficient calcium consumption has also been associated with the depletion of calcium stores in the bone that can potentially weaken the skeletal system in pregnant women. Calcium supplementation, has been associated with a 50% reduction in the risk of developing pregnancy induced hypertension [45] and has been found to reduce uterine smooth muscle contractility and prevent preterm labour and delivery [46].

**Iodine**

Iodine is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), critical for normal growth and the development of most organs, especially the brain. In its natural form, iodine can be found in sea water, marine plants and minerals in the soil. Iodine content in food and water is dependent upon factors such as altitude, rainfall and soil microbes [47].

Iodine plays a critical role in neuropsychological development of the fetus throughout gestation and its role begins at the peri-conception period [48]. The fetus is entirely dependent on the maternal supply of iodine until 13-15 weeks gestation [48], after this time the fetus develops the ability to recycle and reuse iodine but is still ultimately dependent on the maternal supply [49]. The thyroid stores iodine from the diet, and iodine uptake by the thyroid increases during pregnancy. Provided iodine intake is adequate, stores of thyroid hormone will be sufficient to support both mother and fetus, however may decrease to approximately 40% that of preconception levels in cases of iodine deficiency [47,50].

Ensuring adequate iodine status among women of reproductive age has received high priority by the World Health Organisation (WHO), especially for populations in iodine deficient regions [51]. The recommended range of iodine supplementation during pregnancy is

| Magnesium | Copper | Zinc | Calcium | Iodine | Manganese | Selenium | Iron |
|-----------|--------|------|---------|--------|-----------|----------|------|
| RDI       | Female adult | 320 mg/day | 1.2 mg/day | 8 mg/day | 1000 mg/day | 150 mcg/day | 5.0 mg/day | 60 mcg/day | 18 mg/day |
|          | Pregnancy | 350 mg/day | 1.3 mg/day | 11 mg/day | 1300 mg/day | 220 mcg/day | 5.0 mg/day | 65 mcg/day | 27 mg/day |
|          | Upper limit | 350 mg/day | 10 mg/day | 40 mg/day | 2500 mg/day | 1100 mcg/day | NP | 400 mcg/day | 45 mg/day |

Abbreviations: RDI, recommended dietary intake; NP, not possible to set – may be insufficient evidence or no clear level for adverse effects. Values taken from the National Health and Medical Research Council [19]

Table 1: Requirements of trace element intakes in the general population and during pregnancy.
between 200-250 mcg/day increased from 150 mcg/day for the general population and should be administered in the form of potassium iodide as it is more bioavailable. The UL intake of iodine is 1100 mcg/day [18] (Table 1). Urinary iodine concentration (UIC) is the universally accepted measure of iodine status and is an excellent indicator for recent iodine intake [52].

Iodine deficiency can lead to inadequate thyroid hormone production, which can result in disorders such as goitre, hypothyroidism, cretinism, decreased fertility, miscarriage and trophoblastic disorders [53]. It is also well documented that deficiencies of selenium, iron and vitamin A can exacerbate the effects of iodine deficiency [54]. Iodine deficiency disorders can be prevented through supplementation before or during the first three months of gestation [55]. Studies on iodine supplementation during pregnancy have shown a positive impact on maternal and neonatal outcomes such as significant reductions in the rates of prematurity and stillbirths [51]. The benefits of correcting iodine imbalance far outweigh the risks of supplementation, as long as the iodine dose is within the recommended pregnancy specific limits. Caution needs to be taken when selecting prenatal supplement as they vary in iodine content.

Selenium

Selenium in its elemental form is rare, and occurs naturally in a number of inorganic forms, including selenide, selenate and selenite. Selenium is an essential trace element that plays an important role in human health and is well known for its involvement in the synthesis of numerous selenoproteins, including endogenous antioxidants glutathione peroxidase (GPx), thioredoxin reductase (ThxRed), selenoprotein-P [56] and iodothyronine deiodinases [57].

Dietary selenium is obtained from foods such as nuts (especially Brazil nuts), cereals, meat, fish, eggs, dairy products, fruit and vegetables. The selenium content of food is directly dependent upon its bioavailability in the soil and therefore is subject to regional variation. The RDI of selenium for the general population is 60mcg/day with an additional 10mcg recommended during pregnancy and lactation [18] (Table 1).

Pregnancy is associated with a progressive reduction in selenium concentration that is further exacerbated through conditions such as obesity and some other pregnancy specific complications [58-60]. It is hypothesised that the reduction in selenium in maternal plasma expansion, increased transport of selenium to the fetus [61] and as a result of increased utilisation for the synthesis of seleno dependant antioxidant proteins required to combat the increased oxidative demands of pregnancy [62]. Such reductions in selenium concentration during pregnancy combined with regional variations in selenium intake place pregnant women at risk of suboptimal selenium intake [63] and as a result may experience reduced antioxidant enzyme status during pregnancy.

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species and the ability of biological systems to neutralise free radicals. Pregnancy is associated with increased levels of oxidative stress and an increased reliance on antioxidant proteins. A wealth of scientific literature suggests that oxidative stress during pregnancy may play a role in adverse pregnancy outcomes such as spontaneous abortion, miscarriage [64-67], preeclampsia [68], gestational diabetes, premature rupture of membranes (causing preterm birth) and uterine growth restriction [69-73]. GPx and ThxRed are essential antioxidant enzymes that contain selenium in the form of selenocysteine in their active site. Selenium is required for the expression and activity of these enzyme systems and selenium supplementation has been found to increase the activity of these enzymes both in vitro and in vivo [74]. There is substantial evidence that maternal selenium concentration and GPx activities are reduced in pre-eclamptic pregnancies [75,76] so selenium supplementation could reduce placental oxidative stress and thus improve pregnancy outcomes.

Manganese

Manganese is an essential element found in rocks, soil and water. Dietary sources of manganese including wheat, brown rice, spinach, pineapple and soybeans and it is crucial for a number of biological and physiological processes including immune function, regulation of cellular energy, reproduction, digestion, bone growth and blood clotting [77]. Manganese also functions as a cofactor for many enzymatic reactions including amino acid, lipid, protein and carbohydrate metabolism [78]. Its utilisation in the antioxidant manganese superoxide dismutase (Mn–SOD) is well documented for its protection of the placenta from oxidative stress [79]. Manganese therefore plays a critical role in normal prenatal and neonatal development and is vital that mothers are informed about the importance of adequate intake peri and post conception.

The primary source of manganese is through food intake and for the general population the RDI of manganese is 5 mg/day and remains unchanged for pregnant women. Insufficient data is available to set an UL intake of manganese [18] (Table 1). In adults approximately 1-5% of ingested manganese is absorbed, with women absorbing a significantly higher percentage than males [77]. It is generally believed that manganese deficiencies cannot arise in humans because it is widely available in foods commonly eaten, however foods will only contain the amount of manganese that is available in the soil on which it has been grown. Current farming methods have the potential to cause manganese deficiencies and recent global studies have found a particularly low level of manganese in some food samples [80].

Serum manganese levels increase throughout pregnancy [81,82] and it crosses the placenta via active transport mechanisms [83]. Manganese is one of the least studied micronutrients and there is currently minimal data published about supplementation of manganese in human pregnancy [5]. To date studies have shown lower blood manganese concentrations in women delivering growth restricted infants compared to healthy controls, suggesting that manganese may be important in promoting fetal growth [84]. A more recent study reported lower umbilical cord manganese concentration in neonates born to mothers with preeclampsia compared to controls [85].

It is well established that exposure to high doses of manganese can result in elevations in tissue manganese levels. If excessive accumulation of manganese occurs in the central nervous system it can cause Parkinson’s type syndrome referred to as Manganism [77]. Currently there is little known about the effects of excess manganese on the developing human fetus or pregnancy outcomes.

Iron

Iron is an essential component of haemoglobin, myoglobin, cytochromes and enzymes involved in redox reactions. Haemoglobin is important for oxygen transport to tissues and almost two thirds of the body’s iron is found bound to haemoglobin. Wholegrain cereals, meats, fish and poultry are the major contributors of dietary iron intake and the RDI of iron for the general female population is 8-18 mg/day with an UL intake of 45 mg/day [18] (Table 1). Inadequate iron intake can result in varying degrees of deficiency ranging from iron depletion to
iron deficiency anaemia. Ensuring adequate iron intake is particularly important for women in order to supply the increased demand resulting from menstruation and pregnancy. During pregnancy rapid tissue growth, increasing fetal demand and the expansion of maternal red cell mass, causes a fall in haemoglobin concentration with approximately 38% (32 million globally) of pregnant women considered anaemic [86,87]. The RDI of iron during pregnancy increases to 27 mg/day with an UL intake of 45 mg/day [18] (Table 1). Anaemia during pregnancy is defined as a haemoglobin (Hb) value below the lower limits of its normal range (Hb<110 g/L [87]) during the first or third trimester, or lower than 105 g/L during the second trimester. Iron deficiency anaemia is the most common cause of anaemia during pregnancy worldwide [88] and is increasingly associated with multiple pregnancies, teenage pregnancies and high parity pregnancies [89-91]. Well known clinical presentations of iron deficiency anaemia are tiredness, weakness, lethargy and irritability. The fetus is relatively protected from the effects of iron deficiency by up-regulation of placental iron transport proteins [92] but there is some evidence for the association between maternal iron deficiency and adverse pregnancy outcomes such as preterm deliveries and small for gestational age infants [93-97].

International organisations have been advocating routine iron supplementation for pregnant women in areas of high anaemia prevalence, although conjecture still surrounds recommended doses and regimens. Gastrointestinal side effects are the most common adverse effects associated with iron supplementation and may present at upper level intakes. With an established tolerable UL intake based on gastrointestinal side effects of 45 mg/day [98], this is a daily dose much lower than international recommendations of 60 mg/day with an increased dose of up to 120 mg/day in regions considered iron deficient or if the women is anaemic [99]. Iron supplementation has been shown to significantly reduce the risk of low birth weights [100] and improve haemoglobin concentrations in pregnant women, reducing the risk of maternal anaemia and subsequent adverse pregnancy outcomes.

Discussion

During pregnancy the increased metabolic demands on both macro and micro nutrition place significant stress on the maternal physiological system. It is important that women receive adequate micronutrition on a daily basis to reduce the risk of potential adverse pregnancy and fetal outcomes. Focusing on the essential trace elements; magnesium, copper, zinc, calcium, iodine, manganese, selenium and iron, it is clear all play and important role during pregnancy and deficiencies prior to or during gestation may lead to adverse outcomes for both the mother and fetus. Such complication include; anaemia, hypertension, fetal growth restriction, preeclampsia, labour complications and even death.

Regional variations in trace element concentration in food may leave some populations at risk of suboptimal micronutrient status. As a result increasingly significant proportions of women are turning to pregnancy specific micronutrient supplements to provide them with increased folate and support their bodies prior to and during pregnancy. With this in mind it is important to not only consider the role of trace elements in pregnancy but the possible benefits of combining these elements with essential vitamins. Trace elements such as selenium and zinc in combination with vitamins A, B6, B12, C, D, E, folate, have been found to improve immune function and reduce placental oxidative stress and are considered important in supporting the maternal system to deal with the physiological stress of pregnancy [51,101] through the modulation of maternal and fetal metabolism, reductions in inflammation and the support placentation [13].

When the literature supporting the role of micronutrient supplementation during pregnancy is considered more broadly, there is a number of cohort based studies that suggest the use of multivitamin/minerals during pregnancy may significantly reduce the risk of developing preeclampsia [15,17,102,103], preterm delivery [16] and improve pregnancy outcome [104]. This growing body of evidence may be of particular importance to supporting health care practitioners working in maternal health to provide targeted nutritional counselling particularly in populations with reduced baseline micronutrient status. In conclusion, daily supplementation throughout pregnancy with a multivitamin preparation may be an important and cost effective measure to reduce the risk of pregnancy complications associated with suboptimal trace element intakes.

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