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Trace Elements as Potential Biomarkers of Preeclampsia

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Pregnancy is one of the most important physiological processes of human beings. Adequate nutrition of the mother during this stage has great influence on fetal growth and development, the fetus is totally dependent on the mother to get all the nutrients through the placenta. Malnutrition and poor nutrition are associated with deficiency of micronutrients and pregnancy complications as preeclampsia; this hypertensive disease is characterized by an increased of blood pressure, proteinuria, and complication as hemorrhage and stroke, being one of the main causes of maternal death. This article described the daily consumption of the main trace elements required to maintain a healthy pregnancy. Also is described the deficiency of serum concentrations of calcium, phosphorus, iodine, zinc, magnesium, selenium, copper, fluoride; the excess of iron and its association with preeclampsia disease. Also, this review compiles the concentrations reported of trace elements and are compared in pregnant women with and without preeclampsia. Furthermore is reviewed their possible use as biomarkers for detection of preeclampsia during pregnancy.

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1. INTRODUCTION

An adequate supply of minerals and trace elements is of great importance during pregnancy, because these contribute in maintaining a normal physiology of all tissues, including the placenta and proper development of the fetus. Changes in the concentration of these minerals and trace elements are associated with pregnancy complications such as preeclampsia. To support the high demand of nutrients is necessary to increase the consumption of nutritious foods or if applicable or consumption of multivitamins during pregnancy. In a general way, minerals and trace elements involved in vital processes allowing the fetus stay healthy and repair any cellular damage. A pregnant woman can get the most nutrients living a healthy diet that includes fruits, vegetables, bread, whole meal pasta, dairy products, beans, lean meat, poultry and fish. One of the overriding strategies to combat micronutrient deficiencies during gestation is food fortification with vitamins and minerals, however, in emerging countries, the diet is low in content macro and micronutrients [1-4]. Several studies show that micronutrient deficiency and trace elements are associated with complications during pregnancy. In this regard, preeclampsia and obstetric hemorrhages are the leading causes of maternal mortality, so this review focuses on compiling studies showing the trace elements requirements during gestation and the association between trace elements deficiency or excess with preeclampsia and their possible use as markers diagnosis of this disease.

Despite the widely acknowledged importance of some trace elements as iodine, iron, calcium or selenium roles in the physiology of gestation, however, the roles of other elements are being appreciated recently, for example, zinc deficiency has been associated with pregnancy complications, such as preeclampsia [5,6]. Several studies have demonstrated that trace elements contribute in maintaining a redox balance during gestation, important for the correct expression of genes involved in processes of cell migration and invasion during the remodeling of the spiral arteries of the placenta, responsible for the flow of nutrients between mother and fetus. That is why the consumption of these elements is important during pregnancy. In Table 1, the standard daily requirement trace elements in pregnant and non-pregnant are detailed.

2. HYPERTENSIVE DISORDERS OF PREGNANCY

According to the International Society for the Study of Hypertension in pregnancy, Preeclampsia is one of the main hypertensive disorders of pregnancy associated with maternal death worldwide [7-10]. These disorders are classified as follows: Chronic hypertension, gestational hypertension, preeclampsia and eclampsia. Preeclampsia occurs in patients with existing chronic hypertension, It is characterized by the appearance of proteinuria after 20 weeks or an abrupt increase in the known prior basal proteinuria, amount aggravation of HT, neurosensory symptoms in women previously diagnosed with hypertension. This type of hypertensive disorder gets worse maternal-fetal prognosis significantly in women with chronic hypertension [12]. In Table 1, the symptoms of mild and severe preeclampsia were grouped [10]. For all this, early diagnosis is important for a possible prevention, in order to reduce maternal mortality caused by this complication of pregnancy.

Table 1. Characteristics and symptoms of preeclampsia

Parameter	Mild	Severe
Systolic blood pressure	>140 <160 mm Hg	≥160 mm Hg
Diastolic blood pressure	>90 <110 Hg	≥110 mm Hg
Proteinuria 24 hours	≥300 mg ≤ 3 g	≥ 5g
Oliguria ≤500 mL/24h	Absent	Present
Pulmonary edema	Absent	Present
thrombocytopenia	Minimum	Marked
hyperreflexia	Absent	Present
Visual and auditory disorders	Absent	Present
Elevated liver enzymes	Minimum	Marked
hemolysis	Absent	Present

Sources from [7,8,10,48]

3. TRACE ELEMENTS, CELL FUNCTION AND ITS EFFECTS DURING GESTATION

Nowadays, the analytical technologies of high resolution have allowed the accumulation of information about the nutritional and functional role of trace elements, which can be found at concentrations below 250 mg/g in tissue, food or drinking water. The excess or deficiency have been associated as growth or development limiting of the human being, in maintaining the redox balance, proliferation, cell death and cell differentiation that helps to maintain the normal physiology of all tissues, including placenta. During gestation the excess or deficiency of trace elements may contribute in an endothelial tissue dysfunction, causing complications such as preeclampsia. In Table 2, are showed the principal trace elements that have been reported as essential for human beings and requirement per day for pregnant and non-pregnant women. The role of the deficiency or excess of trace elements and its association with preeclampsia has been reported in several studies highlight the importance of some trace elements as iodine, calcium, iron, zinc and magnesium, of which there is extensive information, unlike the role of other toxic elements that are appreciating recently, for example, cobalt, cadmium, fluoride and chromium. It is important to note that a single nutrient deficiency does not usually happen regularly, being more common deficiency of many trace elements. Trace elements are not synthesized by the human body and requirements go from one million of a gram to one thousandth of a gram per day. In Table 3, shown the trace elements and heavy metals that have been associated with preeclampsia, such elements include calcium, iron, phosphorus, iodine, manganese, magnesium, fluoride, cooper, molybdenum, selenium, chlorine, manganese, chromium, zinc, cobalt and cadmium.

But, what is the role of trace elements during gestation?

Next, it is highlighted the participation of trace elements at a cellular level, and involvement during pregnancy.

Table 2. Recommended daily dose per day in pregnant women and non-pregnant

Requirements daily	Non-pregnant	Pregnant
Iron (mg L^{-1}) [19,20]	0.8	4.4-7.5
Calcium (mg L^{-1}) [11,13]	500-800	600-1300
Iodine (µg L^{-1}) [56]	150	150-300
Zinc (mg L^{-1}) [44,45]	12	15-20
Magnesium (mg L^{-1}) [23]	280	400
Selenium (µg L^{-1}) [41]	55	65-100
Cooper (mg L^{-1}) [60]	1.7	3
Fluoride (µg L^{-1}) [64]	3	3-4

Table 3. Concentration of trace elements and heavy metals in serum of pregnant women with or without preeclampsia

Trace/metal elements	Preeclampsia	Normotensive	Reference
Iron (µg L^{-1})	111	69	[22]
Calcium (mg L^{-1})	78	89	[67]
phosphorus (mmol L^{-1})	0.76	0.99	[68]
Iodine (µg L^{-1})*	40	200	[31,51]
Zinc (mg L^{-1})	0.67	1.30	[48,49]
Magnesium (mg L^{-1})	17.5	20	[35]
Selenium (µg L^{-1})	88	104	[39]
Copper (mg L^{-1})	1.55	2.01	[49]
Chlorine (mEq $^{-1}$)	100	104	[69]
Fluoride (µg L^{-1})	ND	3.22	[64]
Manganese (mg L^{-1})	0.072	0.125	[49]
Chromium (µg L^{-1})	ND	39	[64]
Cobalt (µg L^{-1})	1.27	2.23	[63]
Cadmium (µg L^{-1})	0.33	0.29	[63]
Lead (µg L^{-1})	271	182	[70]
Mercury (µg L^{-1})	ND	0.37-4.5	[65]

*ND: Not determined; * determined in urine sample*

3.1 Calcium

It is known that changes in calcium metabolism increases intestinal absorption, in order to provide calcium from mother to fetus, maintaining maternal levels. In pregnant women calcium requirements are between 600-1300 mg L^{-1} per day vs non-pregnant 500-800 mg L^{-1}per day. It has been reported that levels of serum calcium in pregnant women with preeclampsia are lower than in normotensive women [11-13]. Calcium variations cause angiotensin II increase, vascular smooth muscle vasoconstriction, parathyroid hormone release, nitric oxide synthase and prostacyclin decrease [14,15]. It has been reported that levels of serum calcium in pregnant women with preeclampsia are lower than in normotensive women. However it requires a balance between calcium and magnesium to regulate blood pressure, that is, blood vessels need calcium for contraction, and magnesium for muscle relaxation and opening [12,16,17]. The recommended intake of calcium during pregnancy is mg L^{-1} per day has been reported that consumption below this requirement is associated with increased bone loss during pregnancy and development of preeclampsia [18]. Low Calcium has been detected in serum levels 8.22 mg L^{-1} from pregnant women with preeclampsia in comparison with 9.50 mg L^{-1} in normotensive women, this suggest that calcium is a risk factor of preeclampsia [11]. All this evidence show that changes in the concentration of calcium during gestation can be used as preeclampsia biomarker.

3.2 Iron

It is known that iron is an important factor in determining the levels of iron in the preconception stage in women of reproductive age and can be monitored using the serum ferritin, hemoglobin and soluble transferrin receptor in serum, all using colorimetric tests the average requirement during gestation is 4.4 mg per day [19,20], which are obtainable by a diet rich in animal protein or through dietary supplements such as ferrous sulfate or ferrous gluconate [20]. Anemia due to iron deficiency mineral, involved with an increased risk of death from hemorrhage that may occur during childbirth. Iron deficiency and excess is common during gestation and is associated with pregnancy complications due to free radical damage which can lead to endothelium dysfunction. Therefore iron requirements respond due to an increase in red blood cells and fetoplacental growth, however values of 111 µg L^{-1} in serum iron are associated with preeclampsia in comparison with 69 µg L^{-1} in normal pregnant woman with premature births and low birth weight [4,20-22]. These high iron levels increase lipid peroxidation and cause damage to the endothelial tissue [21].

3.3 Magnesium

This essential trace element is needed for a broad variety of physiological functions, changes in magnesium homeostasis is well regulated and conserved. The magnesium requirements are 400 mg L^{-1} per day during pregnancy vs 280 mg L^{-1} per day in no pregnant women [23]. The extracellular magnesium concentration is regulated by the kidney, and small changes in extracellular and intracellular magnesium concentration have major effects on vascular tone, contractility and reactivity [24-26]. During gestation, the vascular endothelium plays a fundamental role in the regulation of vasomotor tone by releasing nitric oxide, prostacyclin 2, and endothelial-derived hyperpolarizing factor. Intraarterial magnesium infusion increases endothelial-dependent vasodilation [27], and also dilates coronary arteries in humans, but these effects appear to be independent of nitric oxide [28]. In addition to, magnesium is part of enzymes involved in redox maintenance acting as a co-enzyme in more than 300 enzymes [29], and magnesium deficiency can also lead to increased production of reactive oxygen species, associated with endothelial dysfunction and preeclampsia [30-33]. Several studies also have suggested the prophylactic use of magnesium sulfate during pregnancy, as anticonvulsant to prevent eclampsia, although there is controversy for use in preeclampsia [34]. Although, the magnesium levels in serum from women with preeclampsia are 17.5 mg L^{-1} in comparison with normotensive women 20 mg L^{-1} [35].

3.4 Selenium

Selenium is another trace element that is an essential component of various seleno-enzymes, which are involved in the defense against oxidative stress thus avoiding damage to the endothelial cells caused by reactive oxygen species. This element has been associated with hypertensive disease of pregnancy [36,37], it has reported a decrease in maternal serum selenium levels in patients with preeclampsia 88 µg L^{-1} compared with women who had a normal pregnancy 104 µg L^{-1} [38,39]. Several reports showed that pregnant women with preeclampsia disease have selenium deficiency concentrations in comparison with normotensive women [37]. Also, there have been reports of decreased selenoprotein production in preeclamptic pregnancy including important endogenous antioxidants, such as glutathione peroxidase and thioredoxin reductase [38,40]. This has led to study whether selenium prophylaxis reduces the risk of preeclampsia. It is proposed during gestation an increase of selenium 10 µg per day in order to maintain adequate levels (100 µg L^{-1} per day) in order to support the increased requirements of the fetus and newborn and prevent preeclampsia disease [41].

3.5 Zinc

This trace element is widely distributed in nature, at cellular level is located in the soluble portion of the cytoplasm and in the human body is very abundant, for example, in the adult the concentration varies between 1 and 2.5 g in all the body. Everyone, zinc, iodine, copper, magnesium and selenium are involved in biochemical processes such as cellular respiration, oxygen utilization by the cell, replication, transcription, translation of the genetic material in the redox balance. That is, the zinc acts as a cofactor and as a member of approximately 200 enzymes, such as aldolases, dehydrogenases, esterase, peptidases, alkaline phosphatase, carbonic anhydrase, superoxide dismutase and DNA and RNA polymerases, which are involved in the maintenance of normal cell physiology. The safety margin or the difference between the toxic dose and the recommended dose is large; however, studies are required to determine the toxicity of zinc [1,5,42,43]. Daily consumption in non-pregnant women is 12 mg per day, while for pregnant women is estimated in 15-20 mg per day. The additional daily need increases during gestation to meet the demands for fetal growth, rising from 0.1 mg per day additional zinc in the first quarter of pregnancy to 0.7 mg per day additional zinc in the fourth quarter [44,45]. Zinc deficiency is associated to alterations in fetal development, birth defects, cardiac malformations, urological, skeletal, brain and palate defects; when the deficiency is associated with mild preterm birth [42,46,47]. Although the prevalence of zinc deficiency is unknown, several studies shown that is associated with complications of pregnancy, childbirth and postpartum [5,6]. The levels of zinc in serum from women with preeclampsia are 0.67 mg L^{-1} in comparison with 1.30 mg L^{-1} in normotensive women [48,49].

3.6 Iodine

In humans, the total iodine concentration range of 30 to 50 mg in all the body, 30% is present in the thyroid gland and thyroid hormones, the rest, in a 60-80% in extra thyroidal tissues such as stomach, mammary gland, prostate, salivary glands, kidney and placenta, in this tissues iodine contribute to maintenance of normal physiology of the cells. At first trimester of gestation, iodine deficiency are related with insufficient production of thyroid hormones, this are involved with alterations in normal nervous system development (causing mental retardation)subclinical manifestations like attention deficit and limitation on weight-height development [50]. Therefore, iodine deficiency is considered a public health problem and is the first cause of preventable mental retardation. Despite the enormous effort to eradicate iodine deficiency, currently it remains a public health problem and its deficiency during pregnancy has negative effects on the development of the fetal nervous system. For example, studies in Turkey detected low levels of iodine in urine of women with severe preeclampsia (40.25 µg L^{-1}) compared to iodine levels presented by normotensive pregnant women (208.9 µg L^{-1}) [30,31,51], in addition to this, iodine deficiency has been associated with low antioxidant status and high oxidative stress [52]. Iodine *per se,* besides being part of the thyroid hormones, also has antioxidant effects and regulates the expression of genes involved in migration processes and trophoblastic invasion as HIF-alpha and Snail [53-55]. Consumption of 150-300 mg per day of iodine for pregnant women is advised to avoid complications related to their deficiency [56].

3.7 Copper

Copper is involved in normal cell function and is part of many enzymes; its deficiency is associated with a decrease in energy production as ATP apart from the functioning of many enzymes and its deficit alters ATP production, lipid peroxidation, hormonal activation, and angiogenesis and causes lung and skeletal abnormalities. During normal pregnancy, copper levels steadily increase in maternal plasma. Its deficit has been associated with increased risk of premature rupture of membranes and preterm birth. Were also observed low levels of copper in premature cord fetuses and increased levels of copper and oxidative stress are associated with the pathology of preeclampsia [42,43,57-59]. Little changes in serum copper levels during gestation has been associated with women with preeclampsia 1.55 mg L^- in comparison with normotensive women 2.01 mg L^- [49]. Copper intake was around 1.7 mg per day compared to the recommended daily safe and adequate amount of 2-3 mg in pregnant women [60].

3.8 Other Elements

Other elements that have been reported during pregnancy and that are associated with preeclampsia are: Phosphorus, chlorine, fluoride, manganese, chromium, cobalt and cadmium. These elements can cross the placental membrane and its presence is associated with perinatal risks such as premature rupture of membranes, prematurity, low birth weight, preeclampsia and fetal death. This is mainly due to neurotoxic effects, interference placental function, increased oxidative stress, inflammation, endothelial dysfunction, down regulation of nitric oxide, changes in chromosomes and DNA damage [61,62]. In pregnant women has been reported that cobalt, cadmium, manganese and chlorine serum levels are 1.27 μg L^{-1}, 0.33 μg L^{-1}, 0.072 mg L^{-1}, 100 mEq^{-1} and 182 μg L^{-1} in women with preeclampsia in comparison with 2.23 μg L^{-1}, 0.29 μg L^{-1}, 0.125 mg L^{-1}, 104 mEq^{-1} and 271 μg L^{-1} in normotensive women [63], respectively. For fluoride and chromium there are no evidence about their levels in women with preeclampsia, however serum levels of fluoride in normotensive pregnant women are 3.22 μg L^{-1}, de 39 μg L^{-1} [64], and for chromium 0.37-4.5 μg L^{-1} [65]. Changes in serum concentrations of these elements can be used as biomarkers for diagnosing pregnancy complications.

4. CAN TRACE ELEMENTS BE USED AS POTENTIAL BIOMARKERS TO PREDICT PREECLAMPSIA?

The evidence in this review indicates that trace elements may be potential biomarkers for the detection of preeclampsia. Existing technology to measure trace elements is sensitive and has the ability to analyze different elements at once. Currently there are several systems and detection techniques including colorimetric, fluoremeter, spectrometry, flame atomic absorption spectrophotometer, electro thermal atomic absorption spectrophotometer that are routinely used for analysis of trace elements. However, one of the most sensitive is inductively coupled plasma optical emission spectrometry for estimation of trace elements for its more sensitivity, low detection limits and multi-element analysis capability.

So that variations in the concentration of the trace elements may be determined in any organic sample, either serum, urine, saliva, etc. Usually the choice of analytical method depends on available instrumentation, laboratory experience and analyte concentration levels and costs. So that variations in the concentration of the trace elements may be determined in any organic sample, either serum, blood, urine, saliva, tissue, etc. There are studies where the analyses of trace elements in serum have been used to determine the severity of preeclampsia [66]. More studies are needed to support the use of trace elements as potential biomarkers of diagnosis, in order to establish prevention strategies during pregnancy to avoid complications during pregnancy, childbirth and postpartum.

5. CONCLUSION

In this review, the evidence indicates that the concentrations of trace elements measured with existing technology is sensitive enough to detect deficiencies or excesses in serum of pregnant women and establish statistically significant associations with preeclampsia. These studies determined that the deficiency of trace elements as calcium, zinc, magnesium, selenium, copper, manganese and the increase of iron are related to preeclampsia, so that they have the potential to be used as biomarkers for predicting preeclampsia and thus take measures to prevent associated complications and prevent infant and maternal mortality.

Although there are several studies indicating a significant association between preeclampsia and trace elements, longitudinal studies are required to determine simultaneously the concentrations of various trace elements along the three trimesters of pregnancy, and detect changes in concentration, and use them as biomarkers of nutritional status of pregnant women, in order to take preventive measures, prophylaxis based, and thus contribute to avoid complications related to excess or deficiency of these micronutrients during pregnancy interventions.

Similarly in pregnant patients with high risk for developing preeclampsia, monitoring of concentrations of trace elements may assist in early detection and allow to health personnel, control measures and prevention for this disease.

Finally, are required basic studies to understand the mechanism of action of trace elements during pregnancy and its role in the pathogenesis of preeclampsia.

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Author has declared that no competing interests exist.

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