

Oral contraceptives and changes in nutritional requirements

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Abstract. – Oral contraceptives (OCs) are a major class of prescription drug, used by a large proportion of women starting from early adolescence. Much research has been conducted to investigate the physiological changes that occur in women who take OCs. These include changes in general health as well as in nutritional needs. In terms of nutrition, several studies investigated whether women on OCs need different amounts of some vitamins and minerals. In particular, a report from the World Health Organization (WHO) points out that the influence of OCs on nutrient requirements is a topic of high clinical relevance and should, therefore, receive great attention. It has been shown that the key nutrient depletions concern folic acid, vitamins B2, B6, B12, vitamin C and E and the minerals magnesium, selenium and zinc. Most research has focused on the levels of these vitamins and minerals in the blood of women who take OCs compared to women who do not. Since women who take OCs not always have adequate diet, may have unhealthy life style or may suffer from pathologies of malabsorption, the possibility to prevent vitamin and mineral deficiencies by taking appropriate dietary supplements should be considered a first-line approach by clinicians.

Key Words:

Oral contraceptive pill, Nutritional requirements, Vitamins deficiency, Micronutrients deficiency, Fluid retention.

Introduction

Development of hormonal contraception marked a revolutionary step in social change that has improved the lives of women and families worldwide. Oral contraceptives (OCs) are currently among the most common used drugs in developed countries¹. Since they became available in 1960 they have influenced the lives of millions of individuals and are now listed among the most effective drugs available.

The most frequently used agents are a combination of drugs containing both an estrogen and a

progestin. This combination is considered to be highly efficacious, with a theoretical effectiveness generally considered 99.9% and a use effectiveness of 97% to 98%. Ethinyl estradiol (EE) and mestranol are the two estrogens used (with ethinyl estradiol being much more frequently used) and several progestins are currently used. The progestins are 19-nor compounds in the estrane or gonane series with vary degrees of androgenic, estrogenic and anti-estrogenic activities that may be responsible for some of their side effects.

Combined OCs act by preventing ovulation². LH and FSH levels are suppressed, a midcycle surge of LH is absent, endogenous steroid levels are diminished, thus ovulation does not occur. While either component alone can be shown to exert these effects in certain conditions, the combination acts synergistically decreasing plasma gonadotropin levels and suppressing ovulation more consistently than either alone. However, progestin-only contraceptives are sufficient to block ovulation in 60% to 80% of cycles. The effectiveness of these preparations is, thus, thought to be due to a thickening of cervical mucus, which decreases sperm penetration, and to endometrial alterations that impair implantation.

Side Effects of OCs

Since the introduction of the first combined hormonal contraceptive in 1960, there have been many developments toward the goal of minimizing side effects and improving compliance without compromising efficacy^{3,4}. The first of these advancements was a decrease in hormone concentrations to the currently used low-dose formulations. OCs combining a progestin with ≤ 35 mcg ethinyl-estradiol (EE) are now standard, with the exception of select circumstances such as in women using antiepileptic drugs⁵. Formulations with EE 20 mcg have further been shown to decrease estrogenic effects such as bloating and breast tenderness without compromising efficacy⁶.

Despite these advances, issues remain associated with the use of combined hormonal contraceptives. The aim of this review is to focus on the more subtle side effects induced by OCs; indeed, there is a plethora of OC-induced nutritional alteration that are less studied and that on our opinion physicians have to be aware of.

OCs Influence on Nutrient Status

Fluid Retention

Sex hormones are known to interfere with the renin-angiotensin-aldosterone system in two ways. First, estrogens strongly stimulate the production of angiotensinogen, leading to increased levels of angiotensin and aldosterone, and sodium retention. Second, progesterone is a potent aldosterone antagonist, which acts on the mineralocorticoid receptor to prevent sodium retention. In combined oral contraceptives, progestogens devoid of anti-mineralocorticoid and antiandrogenic activity are unable to counteract the sodium-retaining effect of the ethinylestradiol component. As a consequence, these preparations may increase fluid retention, and promote related symptoms such as oedema and increased body weight^{7,8}.

Among the treatments that can help to combat fluid retention and oedema it is mandatory to list the evergreen plant named *Centella asiatica*. *Centella asiatica*, also called Gotu Kola, is a plant from southern Asia. It has been used for centuries as a medicinal herb and was referred to in the French pharmacopoeia in 1884, as well as in the ancient traditional Chinese Shennong Herbal more than 2000 years ago⁹. It contains a variety of ingredients, including asiaticoside (a triterpene glycoside), brahmoside and brahminoside (both saponin glycosides), madecassoside (a glycoside with strong anti-inflammatory properties), madecassic acid, thiamine, riboflavin, pyridoxine, vitamin K, aspartate, glutamate, serine, threonine, alanine, lysine, histidine, magnesium, calcium and sodium⁹.

Centella asiatica has beneficial effects on the venous system. Indeed, it has been shown that the total triterpenic fraction of *Centella asiatica* is effective in improving venous wall alterations in chronic venous hypertension and in protecting the venous endothelium¹⁰. Furthermore, it improves the synthesis of collagen and other tissue proteins by modulating the action of fibroblasts in the vein wall, and stimulates collagen remodeling in and around the venous wall. *Centella*

asiatica is active on the microcirculation in venous and diabetic microangiopathy, and can improve signs and symptoms of venous hypertension and edema¹⁰⁻¹². In conclusion, several beneficial actions of *Centella asiatica* on the venous system and connective tissue make the use of this plant very interesting to treat the venous problems and fluid retention induced by OCs.

Vitamins

Folic Acid

Folate is a water-soluble B vitamin (also known as vitamin B₉ or folacin) that occurs naturally in food. Folic acid is the synthetic form of folate that is found in supplements and added to fortified foods. Folate itself is not biologically active, but its biological importance is due to tetrahydrofolate and other coenzymes that play a crucial role as donors and acceptors of a myriad of one-carbon entities required for important enzymatic reactions, including those involved in amino acid metabolism, purine and pyrimidine synthesis and DNA methylation.

A lack of dietary folic acid leads to folate deficiency, which results in reduced DNA synthesis and cell division¹³. Although this will be seen in all dividing cells, the deficiency will be more obvious in cells that rapidly divide, including for example red blood cells, thereby producing anemia, or in cells derived from bone marrow, leading to leukopenia and thrombocytopenia. Particularly serious are the consequences of folate deficiency during early embryogenesis¹³. For instance, the neural tube has a high need of folate for cell differentiation, growth, and closure to form the spinal cord and brain, and folate deficiency during the periconceptual period can induce neural tube defects (NTDs). NTDs arise from failure of embryonic neural tube closure by the fourth week of pregnancy, causing malformations of the brain and spine, being in certain conditions incompatible with life (e.g. anencephaly). NTDs are the most frequent human malformations occurring during pregnancy. Nowadays, it is generally known that folic acid supplementation in the periconceptual period can prevent the majority of NTDs^{14,15}. In addition to NTDs, adequate folic acid intake during pregnancy is associated with a significant reduction of risk for congenital heart defects¹⁶ and orofacial clefts¹⁷. Taken together, the most common effects caused by folate deficiency result in neural tube defects in developing embryos, macro-

cytic anemia, and peripheral neuropathy^{16,18}. Furthermore, a typical consequence of folate deficiency is an elevation in plasma homocysteine which, in turn, is implicated in the etiology of cardiovascular disease^{19,20}.

Starting from the 1960s, a number of studies has led to the hypothesis that the use of OCs negatively impact folate status²¹⁻²⁵. For instance, a study published by Shojania et al on *Lancet* in 1968²⁶ reported that OC users had lower mean serum levels of folate and higher percentage of subnormal folate levels than a control group. They also observed that the mean serum levels of folate in the group using OCs decreased with increasing duration of use of these compounds, and that the folate level returned to baseline levels within 3 months after the women stopped using the OC²⁶. Among the possible mechanisms it has been suggested that these drugs may cause malabsorption of folate polyglutamates, increased excretion of folates in the urine and accelerated metabolism of folates through the induction of microsomal enzymes that require folic acid²⁵.

Several studies confirmed the earlier findings that reported a negative influence of OCs on folate status^{21-25,27,28}; however, other studies yielded to equivocal results²⁹⁻³¹. These discrepancies might be due to potentially confounding variables intrinsic to most of these clinical studies, including differences in dietary intake, compliance with the contraceptive regimen and duration of use, smoking or alcohol exposure and vitamin supplements use³².

Concerning the clinical significance of these reports, despite OCs have been shown to impair folate metabolism and produce some degree of folate depletion, this effect, alone, is unlikely to cause anemia or megaloblastic changes in women who have a good dietary intake of folate and can absorb it properly^{25,32}. Rather, additional contributory factors, such as poor dietary intake of folate or silent malabsorption, should be looked for. However, since it has been found that folate level return to baseline levels within 3 months after women stop using OCs²⁶, dietary supplementation with folic acid should be considered for women who plan a pregnancy immediately after stopping using OCs.

In conclusion, although it is important to conduct further well-designed studies to better investigate the relationship between currently formulated OCs and folate status, folic acid supplementation in women using OCs should be considered.

Vitamin B₂

Vitamin B₂, also known as riboflavin, is a water-soluble vitamin present in most animal and plant tissues³³. It is one of the essential B vitamins, known to be involved in vital metabolic processes in the body, and it is necessary for energy production and normal cell function and growth. In particular, in its coenzyme forms, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), vitamin B₂ plays key metabolic roles in a variety of reactions involving carbohydrates, amino acids and lipids, and in the conversion of folic acid and vitamin B₆ into their active coenzyme forms^{13,33}. Vitamin B₂ is continuously excreted in the urine of healthy individuals, making deficiency relatively common when dietary intake is insufficient. However, vitamin B₂ deficiency is always accompanied by deficiency of other vitamins. Deficiency and sub-optimal levels of vitamin B₂ (which occur in patients with inflammatory bowel disease, chronic alcoholism and Brown-Vialetto-Van Laere syndrome) leads to a variety of clinical abnormalities that include degenerative changes in the nervous system, endocrine dysfunction, skin disorders and anaemia.

Studies about the relationship between OC use and vitamin B₂ status date back to the 1970s. In a work published on *Lancet* in 1974, Sanpitak and Chayutimonkul used the activity of erythrocyte glutathione reductase, a flavine-dependent enzyme, as an index of vitamin B₂ status in women on OC therapy in Thailand. Activity was significantly lower and response to flavine adenine dinucleotide was significantly higher in women taking OCs than in women not on drugs³⁴. Other studies confirmed this early finding by showing that riboflavin deficiency is common in women of child-bearing age and of a low socioeconomic level, and that the use of OCs aggravates the prevalence of deficiency^{35,36}. A later study showed that vitamin supplements produced significant improvement in pre-existing deficiencies of vitamin B₂ in women using low-dosage OCs³⁷. Altogether, these findings suggest that vitamin B₂ supplementation in women taking OCs may be important where vitamin nutrition is poor and in areas where glucose-6-phosphate dehydrogenase deficiency is common³⁸.

Interestingly, it has been shown that vitamin B₂ supplementation in patients with migraine disorder is associated with statistically significant decreases in headache frequency, intensity, duration and medication intake³⁹. Thus, since headache is a very common side effect reported by patients tak-

ing OCs, vitamin B₂ supplementation in these women could be beneficial not only in case of deficiency but also for this latter aspect.

Vitamin B₆

Vitamin B₆ is a water-soluble vitamin that is present in many foods, added to others, and available as a dietary supplement. It is the generic name for six compounds with vitamin B₆ activity: pyridoxine, an alcohol; pyridoxal, an aldehyde; pyridoxamine, which contains an amino group; and their respective 5'-phosphate esters. Pyridoxal 5' phosphate (PLP) and pyridoxamine 5' phosphate (PMP) are the active coenzyme forms of vitamin B₆⁴⁰.

Vitamin B₆ coenzymes participate to a wide variety of physiological functions in the body, being involved in more than 100 enzymatic reactions, mostly concerned with protein metabolism⁴⁰. Both PLP and PMP are involved in amino acid metabolism, and PLP is also involved in the metabolism of one-carbon units, carbohydrates, and lipids⁴¹. Vitamin B₆ also plays a role in the biosynthesis of neurotransmitters; for instance, it is necessary for the conversion of tryptophan to both niacin and serotonin. Consequently, a dietary deficiency of vitamin B₆ may result in low serotonin levels and/or impaired conversion of tryptophan to niacin. Vitamin B₆ is important in maintaining normal levels of homocysteine⁴¹; furthermore, it is involved in gluconeogenesis and glycogenolysis, immune function, and hemoglobin formation⁴¹.

It has been shown that maternal vitamin B₆ status significantly affects neurological development in rats⁴²⁻⁴⁴ and humans⁴⁵. In rats, maternal vitamin B₆ deficiency led to offspring with fewer neurons in the neocortex⁴⁴, reduced synapse number in the extrapyramidal motor system⁴² and decreased brain weight⁴⁶. Furthermore, clinical studies have shown that vitamin B₆ deficiency increases the risk of pregnancy complications^{47,48}. It has been also shown that low plasma levels of vitamin B₆ are associated with heightened risk for arterial and venous thrombosis, and that this association is independent of other risk factors^{49,50}.

One of the earliest reports to investigate the influence of OCs on vitamin B₆ blood levels was undertaken in 1966 by Rose, who found that women taking estrogen-progestin combination agents had evidence of vitamin B₆ deficiency⁵¹. Other works reported an association between OCs and reduction in PLP concentrations⁵²⁻⁵⁴; al-

though some authors do not agree on the relationship between the observed reduction in PLP concentrations and vitamin B₆ deficiency^{55,56}, a recent large-scale population-based study performed in the United States⁵⁴ found that plasma PLP concentration were significantly reduced in 75% of women taking OCs who did not use dietary supplements. Lussana et al⁵² also reported low levels of vitamin B₆ in women taking OCs, and they speculate that, since low vitamin B₆ levels are independently associated with heightened risks for arterial and venous thromboembolism (TE), they could partly account for the increased TE risk of OC users. Altogether, more recent findings from users of currently formulated lower-dose OCs corroborate previous reports and suggest that supplementation may be necessary to maintain adequate vitamin B₆ status in women taking OCs³².

Vitamin B₁₂

Vitamin B₁₂ (also known as cobalamin) is an essential nutrient that plays a significant role in cell metabolism, especially affecting DNA synthesis and regulation, but also fatty acid synthesis and energy production. The active coenzymes methylcobalamin and 5-deoxyadenosylcobalamin are essential for cell growth and replication. 5-Deoxyadenosylcobalamin is a cofactor for the mitochondrial mutase enzyme that catalyzes the isomerization of L-methylmalonyl CoA to succinyl CoA, an important reaction in carbohydrate and lipid metabolism. In contrast, methylcobalamin supports the methionine synthetase reaction, which is essential for normal metabolism of folate¹. Methyl groups contributed by methyltetrahydrofolate are used to form methylcobalamin, which then acts as a methyl group donor for the conversion of homocysteine to methionine. This folate-cobalamin interaction is pivotal for normal synthesis of purines and pyrimidines, and therefore of DNA¹. Humans depend on exogenous sources of vitamin B₁₂, that is only present in foods of animal origin or in dietary supplements. Vitamin B₁₂ deficiency is recognized clinically by its impact on the hematopoietic and nervous systems. The sensitivity of the hematopoietic system relates to its high rate of cell turnover. As a result of an inadequate supply of vitamin B₁₂, DNA replication becomes highly abnormal. Once a hematopoietic stem cell is committed to enter a programmed series of cell divisions, the defect in chromosomal replication induced by vitamin B₁₂ deficiency results in an

inability of maturing cells to complete nuclear divisions while cytoplasmic maturation continues at a relatively normal rate. This results in the production of morphologically abnormal cells and death of cells during maturation, a phenomenon referred to as ineffective hematopoiesis¹. In case of vitamin B₁₂ deficiency, maturation of red cell precursors is highly abnormal (megaloblastic erythropoiesis). Other tissues with high rates of cell turnover (e.g., mucosa and cervical epithelium) also have high requirements for the vitamin¹. As with inadequate maternal folate status, impaired maternal vitamin B₁₂ status is an independent risk factor for NTDs³².

Several studies have found low mean serum vitamin B₁₂ levels in women using OCs, as compared to nonusers^{27,32,52,57-60}.

Although there is a close interrelation between folate and vitamin B₁₂ metabolism, the mechanism that causes low serum levels of vitamin B₁₂ in patients using OCs seems to be different from the one that causes low serum levels of folate as there is no correlation between the levels of those substances, and folate therapy does not correct the low serum levels of vitamin B₁₂ in OC users^{25,59}. The mechanisms by which serum vitamin B₁₂ is reduced in OC users are not fully understood. Shojania et al^{25,59} found that the total vitamin B₁₂ binding capacity of the serum was significantly lower in women using OCs than in nonusers; the levels of transcobalamin I, a glycoprotein serves to protect vitamin B₁₂ from acid degradation in the stomach, were also lower in OC users^{25,59}. Since these authors found that the absorption and the urinary excretion of vitamin B₁₂ in OC users were normal and their lower serum levels of vitamin B₁₂ were not associated with evidence of tissue depletion, the lower total vitamin B₁₂ binding capacity and lower transcobalamin I levels in the serum of the users could explain their low serum levels of this vitamin^{25,59}.

Since pernicious anemia may also occur in women of reproductive age, the low serum vitamin B₁₂ levels of a woman who is taking OCs should not be disregarded.

Vitamin C

Vitamin C is a water soluble vitamin that exists in the reduced [(i.e. AA (ascorbic acid))] and oxidized [DHAA (dehydro-L-ascorbic acid)] forms. The vitamin acts as a cofactor in a variety of critical metabolic reactions that include the synthesis of collagen, carnitine and catecholamine as well as in peptide amidation and

tyrosine metabolism; it is also involved in maintaining metal ions (like iron and copper) in their reduced forms and serves as a scavenger for free radicals. A role for AA in the regulation of CFTR (cystic fibrosis transmembrane conductance regulator)-mediated chloride secretion in epithelial cells has also been suggested⁶¹. Deficiency of this vitamin leads to a variety of clinical abnormalities that include scurvy, poor wound healing, vasomotor instability and connective tissue disorders. With regard to DHAA, this compound is structurally different from AA; rather, it is similar to glucose. DHAA is converted into AA in intestinal epithelial cells via the action of DHAA reductase. Converting DHAA into AA helps maintain a low (non-toxic) level of the compound⁶².

To determine the effect of OCs on vitamin C status, researchers determined the amount of ascorbate in plasma leukocytes, platelets, and whole blood entities. It has been stated that vitamin C levels in platelets and leukocytes are lowered by the use of OCs, specifically those containing estrogen, which is thought to increase the rate of metabolism of vitamin C^{60,63-65}. It has been suggested that the change in the blood levels is the consequence of an alteration in tissue uptake patterns that result in changes in the distribution of the vitamin³⁸.

Other Authors reported that, with adequate dietary intake of ascorbic acid, there is no threat to ascorbic acid status as a result of using OCs for periods of six months to seven years⁶⁶. However, the situation may be different for patients who have poor diet, unhealthy habits or a pathology of malabsorption⁶⁰.

A recent work⁶⁷ reported significant increases in plasma malondialdehyde levels, associated with decreased activities of glutathione peroxidase (GPx) and glutathione reductase (GR) in women taking low-dose OCs compared to the control group, thus indicative of increased oxidative stress induced by the hormonal therapy. Interestingly, supplementation with vitamins C and E significantly increased GPx and GR activity and reduced plasma malondialdehyde levels in women taking low-dose OCs, thus suggesting that supplementation with these vitamins may protect against potential cardiovascular risks induced by contraceptive drugs.

Vitamin E

Vitamin E is a term that encompasses a group of potent, lipid-soluble, chain-breaking antioxi-

dants. Molecules having vitamin E antioxidant activity include four tocopherols (α , β , γ , δ) and four tocotrienols (α , β , γ , δ); among them, α -tocopherol, is the most abundant form in nature and has the highest biological activity⁶⁸. Good food sources of vitamin E include vegetable oils and margarines. Vitamin E is also found in fruits and vegetables, grains, nuts, seeds and fortified cereals.

As an antioxidant, vitamin E acts as a peroxy radical scavenger, preventing the propagation of free radicals in tissues, by reacting with them to form a tocopheryl radical which is then oxidized by a hydrogen donor (such as Vitamin C) and thus return to its reduced state⁶⁹. As it is fat-soluble, it is incorporated into cell membranes, thus protecting them from oxidative damage⁶⁹. Apart its antioxidant properties, vitamin E up-regulates the activities of cytosolic phospholipase A2 and cyclooxygenase. The enhanced activity of these two rate-limiting enzymes in the arachidonic acid cascade provides a mechanism for the observation that vitamin E dose-dependently enhances release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation⁶⁸. Vitamin E plays also an important role in reproductive function: for instance, it has been shown that vitamin E prevents loss of spermatogenesis in males and the failure to retain zygotes in female rats⁷⁰.

Early preclinical studies showed that the administration of contraceptive steroids significantly lowered plasma tocopherol levels and increased dietary requirements for vitamin E in rats⁷¹. A more recent study by Akinsanya et al⁷² investigated the effects of vitamin E and folic acid on the superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) production and glutathione-S-transferase (GST) activities in female Wistar rats treated with combined OCs containing ethinyl estradiol in combination with levonorgestrel. They found that vitamin E and folic acid significantly reduced the increase in antioxidant markers induced by the combined OCs on in rats⁷². In line with preclinical findings, Briggs and Briggs⁷³ showed that combined-type OCs decreased plasma tocopherols in healthy Caucasian women, and, therefore, proposed that women taking these drugs require supplementary vitamin E. In line with this hypothesis, Renaud et al⁷⁴ found that OC users showed significant increase in the clotting activity of platelets and the response to ADP-induced aggregation concomitant with a decrease in plasma vitamin E. After vitamin E administration, platelet activity was markedly decreased, with a significant increase in the level of

vitamin E in plasma and platelets. On the basis of these results, the Authors concluded that the platelet hyperactivity of long term OC users might be dependent on a low level of platelet α -tocopherol which can be rapidly overcome by administering a vitamin E supplement⁷⁴. Thus, it could be speculated whether some of the adverse cardiovascular side effects of OCs are associated with a change in vitamin E status. This issue, however, needs to be further investigated.

Minerals

Zinc

Zinc is an essential mineral that has important biological functions. It is found in several enzymes and has roles in the metabolism of RNA and DNA, signal transduction, and gene expression. It also regulates apoptosis⁷⁵. In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons and plays a key role in synaptic plasticity and learning processes⁷⁶. High concentration of zinc is found in muscle, bones, kidney, liver, in the prostate and parts of the eye. Semen is particularly rich in zinc, which is a key factor in reproductive function⁷⁷.

The zinc status of women using OCs has been of concern since 1968, when it was observed that women using OCs had lower plasma zinc levels than women who were not^{78,79}. Several studies done during the following decades confirmed this finding⁸⁰⁻⁸⁴. It has been thought that the decrease in serum zinc could be reflected in a reduction of tissue zinc status due to changes in zinc absorption, excretion or tissue turnover. If these changes occur, the dietary zinc requirement would be greater in women using OCs⁸⁴.

Selenium

Selenium is a micronutrient that functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidases and certain forms of thioredoxin reductase found in animals and some plants⁷⁷. Selenium also plays a role in the functioning of the thyroid gland and in every cell that uses thyroid hormone, by participating as a cofactor for the three known thyroid hormone deiodinases, which activate and then deactivate various thyroid hormones and their metabolites. It has been shown that selenium supplementation may be beneficial in the Hashimoto's thyroiditis, an autoimmune disease in which the thyroid gland is attacked by a variety of cell- and antibody-mediated immune

processes. Indeed, a reduction of 21% of serum anti-thyroid peroxidase antibodies levels was reported with the dietary intake of 0.2 mg of selenium⁸⁵. Since selenium is an important antioxidant nutrient, deficiency can increase the risk of cancer and cardiovascular disease^{86,87}.

Several studies indicate that OCs interfere with selenium absorption. Heese et al⁸⁸ conducted a study involving 200 female students, half of whom had been taking low-dosage triphasic contraceptive medication for a minimum of 3 months. The differences in mean serum selenium concentrations were statistically significant. Falah et al⁸⁴ also reported lower serum selenium levels in women taking OCs compared to control subjects, although this difference did not reach statistical significance. These findings may be important, since selenium has been suggested to have a beneficial role in the prevention of cancer, especially breast cancer^{89,90}.

Magnesium

Magnesium is an essential element in biological systems⁹¹. For instance, ATP (adenosine triphosphate), the main source of energy in cells, must be bound to a magnesium ion in order to be biologically active. Similarly, magnesium plays a role in the stability of all polyphosphate compounds in the cells, including those associated with DNA- and RNA-synthesis. Over 300 enzymes require the presence of magnesium ions for their catalytic action, including all enzymes utilizing or synthesizing ATP, or those that use other nucleotides to synthesize DNA and RNA⁹¹.

Inadequate magnesium intake frequently causes muscle spasms, and has been associated with cardiovascular disease, diabetes, high blood pressure, anxiety disorders, migraines, osteoporosis and cerebral infarction⁹¹⁻⁹⁴. Deficiency of magnesium may be attributed to decreased dietary consumption and the use of diuretics⁹⁴.

It has repeatedly been shown that serum magnesium levels are reduced by OCs^{83,95-98}. Prophylactic treatment of postmenopausal osteoporosis with oestrogen and calcium has also been shown to reduce serum magnesium levels⁹⁹. When magnesium depletion occurs, it alters the calcium/magnesium ratio which can affect blood coagulability⁹¹. Thus, it has been hypothesized that the reduction in serum magnesium levels is one reason for increased risk of thrombosis while using OCs⁹⁷. On the basis of these data, magnesium supplementation during oral contraception should be considered.

Conclusions

Literature data starting from the 1970s clearly show that OCs induce depletions of nutrients which are likely to contribute to several common side effects. Thus, the possibility to prevent vitamin and mineral deficiencies through the intake of appropriate dietary supplements should be considered as a first line approach by clinicians. The ideal dietary supplement should contain vitamins of the B complex together with folic acid, vitamin E and C as well as minerals such as magnesium, zinc and selenium.

Although these micronutrients are present in many common foods (Table I) it is widely known that there is a difference in bioavailability between dietary supplementation and food intake, due to the different forms in which minerals and vitamins can be found in food and because cooking, storage, and processing usually result in the reduction or loss of their amount. Furthermore, thanks to its beneficial effects on the venous system and fluid retention, *Centella asiatica* may help preventing some of the common side-effects induced by OCs.

Conflict of Interest

None.

Table I.

Micronutrients	Sources	RDA %
Folic acid	Enrtails, green vegetables, legumes, eggs	200 mcg
Vitamin B ₁₂	Meat, milk products, eggs	2.5 mcg
Vitamin B ₆	Animals and vegetable derived food	1.4 mg
Vitamin B ₂	Milk, milk products, liver, vegetables	1.4 mg
Vitamin C	Green vegetables, citrus fruits, tomato	80 mg
Vitamin E	Cereals, fruits and vegetables	12 mg
Zinc	Meat, peanuts, bean, wheat bread	10 mg
Magnesium	Cereals, walnuts, almond, buckwheat, lentils, green vegetables	375 mg
Selenium	Vegetables	55 mcg

References

- 1) BRUNTON LL, BLUMENTHAL DK, MURRI N, DANDAN RH, KNOLLMANN BC. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics. XII ed. New York; 2011.
- 2) LOBO RA, STANCZYK FZ. New knowledge in the physiology of hormonal contraceptives. *Am J Obstet Gynecol* 1994; 170: 1499-1507.
- 3) SHULMAN LP. The state of hormonal contraception today: benefits and risks of hormonal contraceptives: combined estrogen and progestin contraceptives. *Am J Obstet Gynecol* 2011; 205: S9-13.
- 4) MANSOUR D, INKI P, GEMZELL-DANIELSSON K. Efficacy of contraceptive methods: a review of the literature. *Eur J Contracept Reprod Health Care* 2010; 15(Suppl 2): S19-31.
- 5) BITZER J, SIMON JA. Current issues and available options in combined hormonal contraception. *Contraception* 2011; 84: 342-356.
- 6) GALLO MF, NANDA K, GRIMES DA, LOPEZ LM, SCHULZ KF. 20 microg versus >20 microg estrogen combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2011; (1): CD003989.
- 7) OELKERS W. Antimineralocorticoid activity of a novel oral contraceptive containing drospirenone, a unique progestogen resembling natural progesterone. *Eur J Contracept Reprod Health Care* 2002; 7(Suppl 3): 19-26; discussion 42-13.
- 8) SMALS AG. Fluid retention with oral contraceptives. *Gynecol Endocrinol* 2000; 14: 476-478.
- 9) BRINKHAUS B, LINDNER M, SCHUPPAN D, HAHN EG. Chemical, pharmacological and clinical profile of the East Asian medical plant *Centella asiatica*. *Phytomedicine* 2000; 7: 427-448.
- 10) INCANDELA L, CESARONE MR, CACCHIO M, DE SANCTIS MT, SANTAVENERE C, D'AURO MG, BUCCI M, BELCARO G. Total triterpenic fraction of *Centella asiatica* in chronic venous insufficiency and in high-perfusion microangiopathy. *Angiology* 2001; 52(Suppl 2): S9-13.
- 11) DE SANCTIS MT, BELCARO G, INCANDELA L, CESARONE MR, GRIFFIN M, IPPOLITO E, CACCHIO M. Treatment of edema and increased capillary filtration in venous hypertension with total triterpenic fraction of *Centella asiatica*: a clinical, prospective, placebo-controlled, randomized, dose-ranging trial. *Angiology* 2001; 52(Suppl 2): S55-59.
- 12) CESARONE MR, BELCARO G, DE SANCTIS MT, INCANDELA L, CACCHIO M, BAVERA P, IPPOLITO E, BUCCI M, GRIFFIN M, GEROUKAKOS G, DUGALL M, BUCCELLA S, KLEYWEGHT S. Effects of the total triterpenic fraction of *Centella asiatica* in venous hypertensive microangiopathy: a prospective, placebo-controlled, randomized trial. *Angiology* 2001; 52(Suppl 2): S15-18.
- 13) WHO. World Health Organization: Vitamin and mineral requirements in Human nutrition. WHO Library; 1998.
- 14) WALD NJ, BOWER C. Folic acid and the prevention of neural tube defects. *Br Med J* 1995; 310: 1019-1020.
- 15) WALD NJ, GILBERTSON MP. Folic acid in prevention of neural tube defects. *Lancet* 1995; 345: 389.
- 16) MOSLEY BS, CLEVES MA, SIEGA-RIZ AM, SHAW GM, CANFIELD MA, WALLER DK, WERLER MM, HOBBS CA. Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. *Am J Epidemiol* 2009; 169: 9-17.
- 17) SHAW GM, LAMMER EJ, WASSERMAN CR, O'MALLEY CD, TOLAROVA MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995; 346: 393-396.
- 18) MANZOOR M, RUNCIE J. Folate-responsive neuropathy: report of 10 cases. *Br Med J* 1976; 1: 1176-1178.
- 19) SCOTT JM, WEIR DG. Homocysteine and cardiovascular disease. *Quarterly J Med* 1996: 561-563.
- 20) WALD NJ, WATT HC, LAW MR, WEIR DG, MCPARTLIN J, SCOTT JM. Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. *Arch Intern Med* 1998; 158: 862-867.
- 21) TROWBRIDGE M, JR., WADSWORTH RC, MOFFITT E. Malabsorption associated with gluten enteropathy, do oral contraceptives interfere with folate metabolism? *J Maine Med Assoc* 1968; 59: 240-242.
- 22) PATON A. Oral contraceptives and folate deficiency. *Lancet* 1969; 1: 418.
- 23) RYSER JE, FARQUET JJ, PETITE J. Megaloblastic anemia due to folic acid deficiency in a young woman on oral contraceptives. *Acta Haematol* 1971; 45: 319-324.
- 24) WHITEHEAD N, REYNER F, LINDENBAUM J. Megaloblastic changes in the cervical epithelium. Association with oral contraceptive therapy and reversal with folic acid. *JAMA* 1973; 226: 1421-1424.
- 25) SHOJANIA AM. Oral contraceptives: effect of folate and vitamin B12 metabolism. *Can Med Assoc J* 1982; 126: 244-247.
- 26) SHOJANIA AM, HORNADY G, BARNES PH. Oral contraceptives and serum-folate level. *Lancet* 1968; 1: 1376-1377.
- 27) WERTALIK LF, METZ EN, LOBUGLIO AF, BALCERZAK SP. Decreased serum B 12 levels with oral contraceptive use. *JAMA* 1972; 221: 1371-1374.
- 28) PRASAD AS, LEI KY, MOGHISSI KS, STRYKER JC, OBERLEAS D. Effect of oral contraceptives on nutrients. III. Vitamins B6, B12, and folic acid. *Am J Obstet Gynecol* 1976; 125: 1063-1069.
- 29) PRITCHARD JA, SCOTT DE, WHALLEY PJ. Maternal folate deficiency and pregnancy wastage. IV. Effects of folic acid supplements, anticonvulsants, and oral contraceptives. *Am J Obstet Gynecol* 1971; 109: 341-346.
- 30) CASTREN OM, ROSSI RR. Effect of oral contraceptives on serum folic acid content. *J Obstet Gynaecol Br Commonw* 1970; 77: 548-550.
- 31) GREEN TJ, HOUGHTON LA, DONOVAN U, GIBSON RS, O'CONNOR DL. Oral contraceptives did not affect biochemical folate indexes and homocysteine concentrations in adolescent females. *J Am Diet Assoc* 1998; 98: 49-55.

- 32) WILSON SM, BIVINS BN, RUSSELL KA, BAILEY LB. Oral contraceptive use: impact on folate, vitamin B(6), and vitamin B(1)(2) status. *Nutr Rev* 2011; 69: 572-583.
- 33) BRODY T. Riboflavin. ed. N. Biochemistry. San Diego. Academic Press; 1999.
- 34) SANPITAK N, Chayutimonkul L. Oral contraceptives and riboflavine nutrition. *Lancet* 1974; 1: 836-837.
- 35) NEWMAN LJ, LOPEZ R, COLE HS, BORIA MC, COOPERMAN JM. Riboflavin deficiency in women taking oral contraceptive agents. *Am J Clin Nutr* 1978; 31: 247-249.
- 36) BRIGGS M. Letter: Oral contraceptives and vitamin nutrition. *Lancet* 1974; 1: 1234-1235.
- 37) BAMJI MS, PREMA K, JACOB CM, RANI M, SAMYUKTA D. Vitamin supplements to Indian women using low dosage oral contraceptives. *Contraception* 1985; 32: 405-416.
- 38) THORP VJ. Effect of oral contraceptive agents on vitamin and mineral requirements. *J Am Diet Assoc* 1980; 76: 581-584.
- 39) ZENCIRCI B. Comparison of the effects of dietary factors in the management and prophylaxis of migraine. *J Pain Res* 2010; 3: 125-130.
- 40) MCCORMICK D. Vitamin B6. IX ed. Present Knowledge in Nutrition. ed. R.R. Bowman B. Washington DC. International Life Sciences Institute; 2006.
- 41) MACKAY A, DAVIS S, GREGORY J. Vitamin B6. X ed. Modern Nutrition in Health and Disease. M. Shils, Shike M, Ross A, Caballero B, Cousins R, Eds. Baltimore, MD. Lippincott Williams & Wilkins; 2005.
- 42) WASYNCZUK A, KIRKSEY A, MORRE DM. Effects of maternal vitamin B-6 deficiency on specific regions of developing rat brain: the extrapyramidal motor system. *J Nutr* 1983; 113: 746-754.
- 43) WASYNCZUK A, KIRKSEY A, MORRE DM. Effect of maternal vitamin B-6 deficiency on specific regions of developing rat brain: amino acid metabolism. *J Nutr* 1983; 113: 735-745.
- 44) KIRKSEY A, MORRE DM, WASYNCZUK AZ. Neuronal development in vitamin B6 deficiency. *Ann NY Acad Sci* 1990; 585: 202-218.
- 45) CANDITO M, RIVET R, HERBETH B, BOISSON C, RUDIGOZ RC, LUTON D, JOURNEL H, OURY JF, ROUX F, SAURA R, VERNHET I, GAUCHERAND P, MULLER F, GUIDICELLI B, HECKENROTH H, POULAIN P, BLAYAU M, FRANCANNET C, ROSZYK L, BRUSTIE C, STACCINI P, GERARD P, FILLION-EMERY N, GUEANT-RODRIGUEZ RM, VAN OBBERGHEN E, GUEANT JL. Nutritional and genetic determinants of vitamin B and homocysteine metabolisms in neural tube defects: a multicenter case-control study. *Am J Med Genet A* 2008; 146A: 1128-1133.
- 46) AYCOCK JE, KIRKSEY A. Influence of different levels of dietary pyridoxine on certain parameters of developing and mature brains in rats. *J Nutr* 1976; 106: 680-688.
- 47) RONNENBERG AG, VENNERS SA, XU X, CHEN C, WANG L, GUANG W, HUANG A, WANG X. Preconception B-vitamin and homocysteine status, conception, and early pregnancy loss. *Am J Epidemiol* 2007; 166: 304-312.
- 48) RONNENBERG AG, GOLDMAN MB, CHEN D, AITKEN IW, WILLETT WC, SELHUB J, XU X. Preconception folate and vitamin B(6) status and clinical spontaneous abortion in Chinese women. *Obstet Gynecol* 2002; 100: 107-113.
- 49) ROBINSON K, MAYER EL, MILLER DP, GREEN R, VAN LENTE F, GUPTA A, KOTTKE-MARCHANT K, SAVON SR, SELHUB J, NISSEN SE, et al. Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease. *Circulation* 1995; 92: 2825-2830.
- 50) CATTANEO M, LOMBARDI R, LECCHI A, BUCCIARELLI P, MANNUCCI PM. Low plasma levels of vitamin B(6) are independently associated with a heightened risk of deep-vein thrombosis. *Circulation* 2001; 104: 2442-2446.
- 51) ROSE DP. The influence of oestrogens on tryptophan metabolism in man. *Clin Sci* 1966; 31: 265-272.
- 52) LUSSANA F, ZIGHETTI ML, BUCCIARELLI P, CUGNO M, CATTANEO M. Blood levels of homocysteine, folate, vitamin B6 and B12 in women using oral contraceptives compared to non-users. *Thromb Res* 2003; 112: 37-41.
- 53) LUMENG L, CLEARY RE, LI TK. Effect of oral contraceptives on the plasma concentration of pyridoxal phosphate. *Am J Clin Nutr* 1974; 27: 326-333.
- 54) MORRIS MS, PICCIANO MF, JACQUES PF, SELHUB J. Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003-2004. *Am J Clin Nutr* 2008; 87: 1446-1454.
- 55) LEKLEM JE, BROWN RR, ROSE DP, LINKSWILER HM. Vitamin B6 requirements of women using oral contraceptives. *Am J Clin Nutr* 1975; 28: 535-541.
- 56) LEKLEM JE. Vitamin B-6 requirement and oral contraceptive use--a concern? *J Nutr* 1986; 116: 475-477.
- 57) SUTTERLIN MW, BUSSEN SS, RIEGER L, DIETL J, STECK T. Serum folate and Vitamin B12 levels in women using modern oral contraceptives (OC) containing 20 microg ethinyl estradiol. *Eur J Obstet Gynecol Reprod Biol* 2003; 107: 57-61.
- 58) RIEDEL B, BJORKE MONSEN AL, UELAND PM, SCHNEEDE J. Effects of oral contraceptives and hormone replacement therapy on markers of cobalamin status. *Clin Chem* 2005; 51: 778-781.
- 59) SHOJANIA AM, WYLIE B. The effect of oral contraceptives on vitamin B12 metabolism. *Am J Obstet Gynecol* 1979; 135: 129-134.
- 60) VENINGA KS. Effects of oral contraceptives on vitamins B6, B12, C, and folacin. *J Nurse Midwifery* 1984; 29: 386-390.
- 61) FISCHER H, SCHWARZER C, ILLEK B. Vitamin C controls the cystic fibrosis transmembrane conductance regulator chloride channel. *Proc Natl Acad Sci U S A* 2004; 101: 3691-3696.
- 62) SCHELL DA, BODE AM. Measurement of ascorbic acid and dehydroascorbic acid in mammalian tissue utilizing HPLC and electrochemical detection. *Biomed Chromatogr* 1993; 7: 267-272.

- 63) MATSUI MS, ROZOVSKI SJ. Drug-nutrient interaction. *Clin Ther* 1982; 4: 423-440.
- 64) WEBB JL. Nutritional effects of oral contraceptive use: a review. *J Reprod Med* 1980; 25: 150-156.
- 65) WHO. *Advances in Methods on Fertility Regulation*. World Health Organization, 1975.
- 66) HUDIBURGH NK, MILNER AN. Influence of oral contraceptives on ascorbic acid and triglyceride status. *J Am Diet Assoc* 1979; 75: 19-22.
- 67) ZAL F, MOSTAFAVI-POUR Z, AMINI F, HEIDARI A. Effect of vitamin E and C supplements on lipid peroxidation and GSH-dependent antioxidant enzyme status in the blood of women consuming oral contraceptives. *Contraception* 2012; 86: 62-66.
- 68) BRIGELIUS-FLOHE R, TRABER MG. Vitamin E: function and metabolism. *FASEB J* 1999; 13: 1145-1155.
- 69) TRABER MG, STEVENS JF. Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radic Biol Med* 2011; 51: 1000-1013.
- 70) EVANS HM, BISHOP KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 1922; 56: 650-651.
- 71) AFTERGOOD L, ALFIN-SLATER RB. Oral contraceptive-alpha-tocopherol interrelationships. *Lipids* 1974; 9: 91-96.
- 72) AKINSANYA MA, ADENIYI TT, AJAYI GO, OYEDELE MA. Effects of vitamin E and folic acid on some antioxidant enzymes activities of female Wistar rats administered combined oral contraceptives. *African J Biochem Res* 2010; 4: 238-242.
- 73) BRIGGS M. Letter: vitamin E status and oral contraceptives. *Am J Clin Nutr* 1975; 28: 436.
- 74) RENAUD S, CIAVATTI M, PERROT L, BERTHEZENE F, DARGENT D, CONDAMIN P. Influence of vitamin E administration on platelet functions in hormonal contraceptive users. *Contraception* 1987; 36: 347-358.
- 75) HAMBIDGE KM, KREBS NF. Zinc deficiency: a special challenge. *J Nutr* 2007; 137: 1101-1105.
- 76) NAKASHIMA AS, DYCK RH. Zinc and cortical plasticity. *Brain Res Rev* 2009; 59: 347-373.
- 77) WAPNIR RA. *Protein Nutrition and Mineral Absorption*. Boca Raton, Florida. CRC Press; 1990.
- 78) HALSTED JA, HACKLEY BM, SMITH JC, JR. Plasma-zinc and copper in pregnancy and after oral contraceptives. *Lancet* 1968; 2: 278-279.
- 79) KING JC. Do women using oral contraceptive agents require extra zinc? *J Nutr* 1987; 117: 217-219.
- 80) BRIGGS MH, BRIGGS M, AUSTIN J. Effects of steroid pharmaceuticals on plasma zinc. *Nature* 1971; 232: 480-481.
- 81) PRASAD AS, OBERLEAS D, MOGHISSI KS, LEI KY, STRYKER JC. Effect of oral contraceptive agents on nutrients: I. Minerals. *Am J Clin Nutr* 1975; 28: 377-384.
- 82) PREMA K, RAMALAKSHMI BA, BABU S. Serum copper and zinc in hormonal contraceptive users. *Fertil Steril* 1980; 33: 267-271.
- 83) AKINLOYE O, ADEBAYO TO, OGUNTIBEJU OO, OPARINDE DP, OGUNYEMI EO. Effects of contraceptives on serum trace elements, calcium and phosphorus levels. *West Indian Med J* 2011; 60: 308-315.
- 84) FALLAH S, SANI FV, FIROOZRAI M. Effect of contraceptive pill on the selenium and zinc status of healthy subjects. *Contraception* 2009; 80: 40-43.
- 85) MAZOKOPAKIS EE, PAPADAKIS JA, PAPADOMANOLAKI MG, BATISTAKIS AG, GIANNAKOPOULOS TG, PROTOPAPADAKIS EE, GANOTAKIS ES. Effects of 12 months treatment with L-selenomethionine on serum anti-TPO Levels in Patients with Hashimoto's thyroiditis. *Thyroid* 2007; 17: 609-612.
- 86) KNEKT P, MARNIEMI J, TEPPLO L, HELIOVAARA M, AROMAA A. Is low selenium status a risk factor for lung cancer? *Am J Epidemiol* 1998; 148: 975-982.
- 87) RUSSO MW, MURRAY SC, WURZELMANN JI, WOOSLEY JT, SANDLER RS. Plasma selenium levels and the risk of colorectal adenomas. *Nutr Cancer* 1997; 28: 125-129.
- 88) HEESE HD, LAWRENCE MA, DEMPSTER WS, POCOCK F. Reference concentrations of serum selenium and manganese in healthy nulliparas. *S Afr Med J* 1988; 73: 163-165.
- 89) CANN SA, VAN NETTEN JP, VAN NETTEN C. Hypothesis: iodine, selenium and the development of breast cancer. *Cancer Causes Control* 2000; 11: 121-127.
- 90) REJALI L, JAAFAR MH, ISMAIL NH. Serum selenium level and other risk factors for breast cancer among patients in a Malaysian hospital. *Environ Health Prev Med* 2007; 12: 105-110.
- 91) COWAN JA. *Introduction to the biological chemistry of magnesium*. ed. J.A. Cowan. New York. VCH; 1995.
- 92) LARSSON SC, VIRTANEN MJ, MARS M, MANNISTO S, PIETINEN P, ALBANES D, VIRTAMO J. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Arch Intern Med* 2008; 168: 459-465.
- 93) STEPURA OB, MARTYNOW AI. Magnesium orotate in severe congestive heart failure (MACH). *Int J Cardiol* 2009; 131: 293-295.
- 94) GUMS JG. Clinical significance of magnesium: a review. *Drug Intell Clin Pharm* 1987; 21: 240-246.
- 95) HAMEED A, MAJEED T, RAUF S, ASHRAF M, JALIL MA, NASRULLAH M, HUSSAN A, NOREEN R. Effect of oral and injectable contraceptives on serum calcium, magnesium and phosphorus in women. *J Ayub Med Coll Abbottabad* 2001; 13: 24-25.
- 96) STANTON MF, LOWENSTEIN FW. Serum magnesium in women during pregnancy, while taking contraceptives, and after menopause. *J Am Coll Nutr* 1987; 6: 313-319.
- 97) OLATUNBOSUN DA, ADENIYI FA, ADADEVOH BK. Effect of oral contraceptives on Serum magnesium levels. *Int J Fertil* 1974; 19: 224-226.
- 98) BLUM M, KITAI E, ARIEL Y, SCHNIERER M, BOGRAD H. Oral contraceptive lowers serum magnesium. *Harefuah* 1991; 121: 363-364.
- 99) SEELIG MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. *Magnes Res* 1990; 3: 197-215.