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Counteracting side effects of combined oral contraceptives through the administration of specific micronutrients

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Abstract. – OBJECTIVE: The occurrence of side effects related to the use of combined oral contraceptives (COCs) – or even the fear of them – often affects patients' compliance and their quality of life. Such adverse effects include both physical and psychological alterations. Therapies based on COCs are related to lower levels of vitamins and minerals, including vitamins B, C and E, zinc, magnesium, and selenium. This review gathers scientific evidence about the effectiveness of the administration of specific micronutrients to address nutritional needs and recover adverse conditions.

MATERIALS AND METHODS: We reviewed literature searching through different databases (MEDLINE, Scopus, Google Scholar). We used different keywords, including micronutrients, COCs, side effects, B vitamins, vitamin C, vitamin E, vitamin D, zinc, magnesium, selenium and Centella Asiatica. We narrowed the search down to English literature, including both preclinical and clinical studies. The outcome of database search was to highlight beneficial effects of specific micronutrients on the evaluated side reactions.

RESULTS: Based on the collected evidence, dietary supplementations of specific micronutrients, whose depletion occurs during COC treatments, have significant beneficial effects. By acting on different aspects and pathways, such supplementation prevents and counteracts discomforts and side effects related to COC treatments.

CONCLUSIONS: Considering the wide use of OCs, taking appropriate dietary supplements could be an effective approach in clinical practice, tailoring therapies and improving both safety and tolerability.

Key Words:
Micronutrients, COCs, Side effects, B vitamins, Vitamin C, Vitamin E, Vitamin D, Zinc, Magnesium, Selenium, Centella Asiatica.

Introduction

Combined oral contraceptive (COC) pills represented a revolutionary step by improving quality of life (QoL) of millions of individuals worldwide. Since the first approval by Food and Drug Administration (FDA) in 1960, their use has spread exponentially overtaking other reversible methods of contraception[1,2]. The oral contraceptives (OCs) represent a convenient, effective, and relatively safe method for birth control, widely used by women during reproductive age[3]. Interestingly, even if their primary intended use is birth control, COCs find to date various medical applications defined as "off-label". For instance, women find relief from such therapies during menopause and in the treatment of gynecological conditions like endometriosis or polycystic ovary syndrome with related acne, hirsutism, and menstrual cycle ailments (painful menstruation, dysmenorrhea and menstrual migraines)[4].

However, even though COCs are among the most prescribed drugs, with more than 100 million users worldwide[5], various side effects may occur during their assumption, most of which may correlate to nutritional deficiency of vitamins and minerals[6-9].

The most frequently used pills consist of a combination of both a progestin and an estrogen, typically ethinyl estradiol, exhibiting an actual effectiveness between 97 and 98%[10]. Such combined formula relies on multiple mechanisms of action related to the hormonal components: (i) they may suppress pituitary gonadotropin secretion, both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by inhibiting ovulation and (ii) they can increase viscosity of the cervical mucus by reducing receptivity of the endometrium to implantation[11]. The combined formulation guarantees a synergic action decreasing plasma gonadotropin levels and suppressing ovulation more effectively than either alone.

The first used COCs contained higher concentration of hormones, thus exposing patients to intolerable side effects, like irregular bleeding, nausea, headache[12]. Indeed, although numerous

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health benefits, COCs exhibit a poor compliance and tolerability due to such adverse effects or even the fear of them[13]. For this reason, since their commercial availability, OCs underwent several modifications regarding dosage, formulation and regimen, with the aim to reduce negative effects and health risks and to improve patients' compliance[14].

Side Effects of COCs: Poor Compliance and Fear of Them

Although COCs are a safe and effective method used in fertility control and in the above-mentioned pathological conditions, over the years OC users experienced several drawbacks and warnings on risks. COCs indeed give rise to problems of clinical tolerability related to the occurrence of various side effects that threaten patients' compliance with a low continuation rate of the therapy.

Furthermore, some of the negative effects of COCs may strongly influence the self-perception of body image with psychological implications influencing self-esteem. Such effects include cellulite and water retention, leg swelling, breast tenderness, increase of body weight. These physical alterations along with the deficiency of some micronutrients, including specific vitamins and minerals, may also strongly impact the mental wellbeing of women taking COCs[15,16].

The increased retention of body fluids is one of the major adverse effects of hormonal therapies[17]. Indeed, sex hormones can directly interfere with the renin-angiotensin-aldosterone system, which is responsible of the whole-body hydro saline balance. Estrogens and progestogens have opposite effects in this regard: estrogens activate the renin-angiotensin system, stimulating the production of angiotensinogen and leading to higher levels of angiotensin, aldosterone and sodium in plasma (sodium retention)[18-20], thus resulting in increased water retention; on the other hand, progesterone is a potent aldosterone antagonist[21], which stimulates the mineralocorticoid receptor preventing sodium retention. Indeed, elevated levels of aldosterone lead to sodium retention and promote potassium efflux inducing fluid retention; on the contrary progesterone, by inhibiting aldosterone receptor, may reduce sodium retention and improve fluid retention itself. However, in the COCs, progestogens are insufficient to counteract sodium-retaining effect of the ethinylestradiol component. Consequently, in these preparations, estradiol causes fluid retention[22] associated with symptoms such as oedema, increased body weight, breast tenderness, leg swelling, and cellulite[5,19,20]. The latter is nothing more than the macroscopic manifestation of alterations of blood and lymphatic vessels and, as well as other physical blemishes, represents a worrisome social issue, encompassing psychological aspects[23].

Notably, side effects of COC administration extend beyond physical aspect: depressive symptoms are indeed one of the most reported reasons for discontinuation and some studies[24-26] investigated depressive mood related to oral contraceptive use. A pilot study indicated that women taking COCs experience more depressive symptoms, both subjectively and objectively measured, compared to non-COC users[25]. Body changes such as increased weight, cellulite and fluid retention can affect self-esteem and self-perception, resulting in depressive mood. The altered perception of body image may cause insecurity and self-esteem issues in these women.

Along with this, also nutritional deficiency of some vitamins and minerals, which may occur during treatments with COCs, can directly contribute to the occurrence of depressive symptoms[10,27]. Several studies[28,29] highlighted that low serum levels of vitamins, especially vitamin B6, and minerals including magnesium, zinc and selenium, correlate with the onset of depressive symptoms.

The increased body weight is another common side effect frequently reported among COC users[30]. Hormonal contraceptives may alter lipid profile and affect cardiovascular risk by inducing dyslipidemia and by increasing Body Mass Index (BMI)[31]. In addition, their use may expose to deficiency of micronutrients such as antioxidants, vitamins, selenium, zinc, generally associated with obesity[32,33]. Weight gain may also result from fluid retention itself, muscle mass gain, fat deposition or a combination of such elements[34,35], and it may seriously influence the continuation rate of COCs, reaching 40% discontinuation in women who gained weight compared to those who kept the same weight[36].

Beyond the above-mentioned effects, the administration of COCs is often accompanied by migraine and lack of energy. In particular, migraine is one of the most common side effects that cause therapy drop-out, especially in those patients who experience low clinical tolerability[37]. As a matter of fact, some evidence revealed that the use of such therapies may exacerbate pre-existing headache or contribute to trigger new episodes, thus confirming the well-recognized role of female hormones in the pathogenesis of migraine[38,39].

Other common side effects include a decrease in libido and a higher incidence of vaginal discharge[40,41] and the risk of venous thromboembolism[42,43]. Several

studies[15,44,45] investigated mechanisms underlying an increased risk for thromboembolism in women taking OCs compared to non-users. Most of them reported increased plasma levels of procoagulant factors and/or decreased levels of anticoagulant proteins[46,47]. Other factors are low plasma levels of those vitamins involved in homocysteine metabolism, such as folate, vitamin B6 and B12[15,48,49], and vitamin E, which is involved in reducing platelet overactivity[50].

Regarding sexual influence, previous studies[51,52] demonstrated that anovulation and irregular menstrual cycle may negatively impact desire, libido and sexual satisfaction, by inducing for example vaginal dryness and lubrification issues[11,53,54].

Overall, considering the wide use of COC therapies, the possibility to reduce side effects' occurrence and severity catches the eye for improving patients' compliance and QoL. A population-based survey reported that about 64.6% of women discontinued oral contraceptives due to side effects[41]. Indeed, even though COC regime and formulation may be tailored on patients' needs, discontinuation still remains a major drawback in therapies.

Dietary Supplementations

The warning label of some OCs clearly indicates that such treatments can influence patients' nutritional status. The World Health Organization (WHO) even highlighted the influence of OCs on nutrient requirements as highly relevant clinical topic[55]. Nutrient depletion mostly concerns vitamins like folic acid, vitamins B2, B6, B12, vitamin C and E and minerals such as magnesium, selenium and zinc. Treatments based on OCs induce changes in women's general health as well as in nutritional intake, often exposing them to side effects. Various studies[15,16,56,57] revealed that women taking OCs exhibit lower blood levels of these vitamins and minerals than non-users, suggesting that they may need to take higher amounts. Therefore, one should consider taking appropriate dietary supplements as a first-line approach to combine with OCs in clinical practice[10].

In this regard, a recent study by Porcaro et al[5] revealed that the administration of a dietary supplement containing vitamins and minerals in patients taking COCs positively impacts the above-mentioned side effects, improving their QoL. The authors observed that a 3-month supplementation with a combination of Centella Asiatica, vitamins B, C and E, and minerals, like magnesium, zinc and selenium, induced significant beneficial effects. They evaluated collateral effects of COCs such as cellulite, leg swelling, breast tenderness, body weight, mood, migraine, fatigue, hair dryness and vaginal discharge.

Overall, in light of these results, we gathered evidence about effectiveness of such dietary supplementation in preventing and recovering discomforts and side effects induced by COCs.

Centella Asiatica

Centella Asiatica (C.A.), also known as Gotu Kola, is a native plant of the Southern Asia, generally considered as an adaptogen and used in Ayurvedic and Chinese medicine[58] as remedy for various diseases[59].

C.A. extract contains a broad spectrum of phytonutrients that provide several beneficial effects, including: (i) pentacyclic triterpenes, which are the main pharmacologically active components[60,61], (ii) vitamins (thiamine, riboflavin, pyridoxine, vitamin K), (iii) amino acids (aspartate, glutamate, serine, threonine, alanine, lysine, histidine), and (iv) minerals (magnesium, calcium, and sodium)[59].

As previously mentioned, a recent clinical study on 26 patients taking OCs revealed the effectiveness of a dietary supplementation containing C.A. extract in counteracting related side effects, including fluid retention, cellulite, oedema, legs swelling[5]. Evidence in literature reports positive effects of C.A. on the venous system, suggesting its role in improving varicose veins, chronic venous insufficiency and diabetic microangiopathy. In particular, C.A. extract contains asiaticoside and bioflavonoids, which stimulate angiogenesis and increase the elasticity of blood vessels[62], ameliorating local microcirculation. In this way, improved perfusion of lower limbs prevents water retention, edema and leg swelling[63], also reducing plasma pressure and breast tenderness[64]. Incandela et al[65] discovered that the total triterpenic fraction of C.A. extract (TTFCA) is effective in improving the microcirculation in diabetic microangiopathy and neuropathy, avoiding the progression toward more serious clinical stages.

The C.A. acts also on connective tissue of the vascular wall improving microcirculatory parameters and decreasing capillary filtration rate, thus recovering venous insufficiency[66-68]. The extract components of C.A. may improve the synthesis of collagen and other connective proteins by modulating the action of fibroblasts in the vein wall and stimulating collagen remodeling in and around venous wall. In line with this, a clinical study by De Sanctis et al[66] confirmed that the TTFCA may im-

prove the capillary filtration rate and ankle edema in patients suffering from venous hypertension. Such properties make C.A. appealing in counteracting fluid retention induced by OCs.

Furthermore, thanks to the activity on collagen, C.A. found novel applications in western medicine and in cosmetic field, especially for treating skin defects such as burns and wounds[69]. It stimulates synthesis of collagen and mucopolysaccharide with beneficial effects on scars and stretch marks, along with positive effects on psoriasis and minor wounds, working as an analgesic and anti-inflammatory agent[70].

Concerning depressive symptoms occurring during OC treatments, C.A. ameliorates the management of anxiety disorder by reducing stress and depressive mood[71]. The terpenic fraction exhibited neuroactive and neuroprotective activities in different experimental models[72]. *In vitro* studies on rat brains[73] demonstrated that C.A. extracts modulate the synthesis of gamma-aminobutyric acid (GABA), which is a neurotransmitter acting on the central nervous system (CNS) in mammals and whose depletion may lead to anxiety and depression[74]. Preclinical studies on healthy rodents[75], as well as on chronically stressed mice[76,77], revealed that C.A. extract improves neurobehavior acting as sedative and anxiolytic agent[78,79].

Overall, C.A. exhibits various beneficial effects on wound healing[58], depression[80], neuroprotective activity[81] and fluid retention[82]. Such properties make the use of this plant extract useful and intriguing to recover side effects induced by OC use.

B Vitamins

The use of OCs often correlates with impaired status of nutrients, including B vitamins, whose deficiency is related to the occurrence of several side effects in COCs users.

Specifically, various studies[15,83,84] reported lower concentrations of vitamins B6, B12 or folate in OC users compared to controls. A work published by Green et al[85] reported that levels of vitamin B12 in OC users were 33% lower than in non-users. Another study revealed a correlation between deficiency of vitamin B12 and increased incidence of neurological disorders[86], and between deficiency of vitamin B6 and anemia, depression, and confusion.

Since women often suspend OC treatments specifically to seek pregnancy, recovering deficiency of B vitamins is crucially important and strongly recommended, as they play pivotal roles also in fetal development[5,87].

Folate (Folic Acid)

Also known as vitamin B9, folate is a water-soluble vitamin. As reported in several studies, the use of COCs negatively impacts folate status, by impairing the uptake pathway and decreasing serum levels. A study performed on women taking OCs revealed a significantly lower serum folate mean level compared with a control group[88,89]. Other studies confirmed this evidence describing the reduction of folate polyglutamate adsorption in OC users[90], probably due to increased metabolism and urinary excretion of folate itself[89].

Folate deficiency affects cellular processes of DNA synthesis and cell division[55], and this aspect is enhanced in those cells that rapidly divide, as red blood cells or cells derived from bone marrow, thus determining anemia or leukopenia and thrombocytopenia. Despite the use of OCs induces various degree of folate depletion, women with a correct dietary intake of folate are unlikely to develop anemia[16,89], unless they present additional factors such as malabsorption of vitamin B9.

Folate deficiency requires a particular focus since it seriously compromises the physiological process of embryogenesis: folic acid supplementation during pregnancy is associated with a significant reduction of the risk for neural tube defects (NTDs), congenital heart defects and orofacial clefts[91]. Considering that pregnancies may occur shortly after the interruption of OC treatments, maintaining physiological folate levels is critical in women of child-bearing age.

In addition, low folate intake also influences homocysteine levels and causes hyperhomocysteinemia, which affects female fertility and increases the risk of cardiovascular diseases. Folate metabolism itself comprises several reactions highly dependent on other vitamins, including vitamin B12, B6 and B2[5]. In particular, they all play a central role in homocysteine metabolism: the use of OCs is associated with low circulating levels of such vitamins and with higher levels of homocysteine[15]. For this reason, supplementation with folic acid in women taking COCs is strongly recommended, along with supplementation with other B vitamins, like vitamin B6, B2, B12, whose adsorption appears equally reduced in these women[15,87].

Vitamin B12

Vitamin B12, also known as cobalamin, plays a central role in cell metabolism, especially in pro-

cesses of DNA synthesis, fatty acid synthesis and energy production. In humans the levels of vitamin B12 directly depend on dietary uptake from food or dietary supplements.

As previously mentioned, levels of vitamin B9 and B12 are strictly related. Vitamin B12, as cofactor of methionine synthase, is involved in maintaining plasma levels of folate[1]: it sustains the transfer of a methyl group derived from vitamin B9 during the physiological conversion of homocysteine to methionine[92]. Lower levels of vitamin B12 determine the accumulation of methylated form of folic acid (5-MTHF) acting as "methyl trap", thus causing increased levels of homocysteine. Beside affecting folate metabolism, deficiency of vitamin B12 is to date recognized as an independent risk factor for the occurrence of NTDs and anemia, and it is clinically relevant for its negative impact on hematopoietic and nervous systems[10]. Various evidence further described clinical relevance of vitamin B12, especially in the CNS: its deficiency may result in increased fatigue, nerve damage, and developmental delay[93].

Several studies reported that serum levels of vitamin B12 are lower in OC users than controls[57,84,89,94]. For example, Green et al[85] in 1998 observed that levels of vitamin B12 in OC users were 33% lower than non-users. Interestingly, vitamin B12 supplementation can prevent headache occurring as a common side effect of COCs by scavenging nitric oxide[95,96], which represents an independent cause of migraine attacks[97,98].

Vitamin B2

Vitamin B2, also known as riboflavin, is one of the essential B vitamins and it plays a central role in several biological processes including conversion of folic acid and vitamin B6 into their active form[55,99]. Sanpitak et al[100], by measuring the activity of erythrocyte glutathione reductase, demonstrated that levels of vitamin B2 are lower in women taking OCs.

Reduced levels of vitamin B2 may correlate with migraine episodes, which are frequently reported as side effect of OCs causing therapy discontinuation. Migraine's etiology involves a reduction in metabolism of mitochondria, which requires vitamin B2 for the electron transport chain and the biosynthesis of ATP and cell energy production. Previous studies revealed that supplements with vitamin B2 are effective in migraine prophylaxis, and in reducing frequency, intensity and duration of headaches, thus improving migraine episodes[101,102]. Specifically, a controlled study on 55 patients revealed that a 3-month supplementation with vitamin B2 significantly reduced migraine episodes and duration, confirming its beneficial effect[103,104].

Vitamin B6

Vitamin B6 is present in many foods, and it is available as dietary supplement. It acts as a coenzyme in several enzymatic reactions associated with different physiological functions including the conversion of tryptophan to niacin and serotonin. Tryptophan metabolism is abnormal in OC users, and it represents an indirect measure of vitamin B6 status, indeed supplementation with vitamin B6 can recover physiological tryptophan levels[105-108].

However, as estrogens may influence tryptophan metabolism independently of vitamin B6[16,107], one should consider other metabolites of vitamin B6 as markers to study the effects of OCs. They include plasma pyridoxal 5′-phosphate (PLP), urinary 4-pyridoxic acid (4-PA), urinary B6, and erythrocyte aminotransferase or transaminase activity. Interestingly, also PLP is significantly reduced in OC users in both fasting and non-fasting plasma compared to non-users[15,109], confirming reduced levels of vitamin B6 in these women.

Several studies reported that COCs negatively influence women's mood by reducing the adsorption of micronutrients like vitamin B6[10,27]. A recent review from Wang et al[29] revealed that micronutrient deficiencies may play a crucial role in the development of depression, opening a new therapeutic field to dietary supplements. Kafeshani et al[110] demonstrated in a study on 3000 individuals that inadequate intake of vitamin B6 is related to an increased risk of anxiety and depression. Indeed, vitamin B6 supplementation exhibits beneficial effects on emotional symptoms, such as reducing irritability, depression and tiredness[111]. Previous studies reported that supplementation improves clinical symptoms of B6 deficiency and reduces side effects in OC users[112,113].

Vitamin B6 may also modulate magnesium levels[114,115]: as both participate in neurobiological mechanisms, one should hypothesized a synergistic effect of such micronutrients[116]. A randomized trial including a hundred women taking COCs revealed that daily assumption of vitamin B6 may reduce the severity of symptoms like headache and dizziness compared to placebo[112].

Finally, vitamin B6 is involved in the management of breast tenderness. As demonstrated in a work by Shobeiri et al[117] both vitamin B6 and vitamin E exhibit similar effects in reducing breast pain in 80 patients suffering from cyclic mastalgia. Other recent studies

confirmed such data indicating the positive effect of vitamin B6 in relieving breast pain[117,118].

Vitamin B8

Vitamin B8, also known as biotin, is a water-soluble vitamin acting as prosthetic group of carboxylases. It also modulates the expression of genes involved in the regulation of intermediary metabolism, such as those favoring hypoglycemia, like insulin, insulin receptor, pancreatic and hepatic glucokinase[119], and it is involved in processes like development[120,121] and immunity[122]. At the same time, vitamin B8 contributes to glucose production in liver by decreasing the expression of hepatic phosphoenolpyruvate carboxykinase, a key gluconeogenic enzyme that stimulates glucose production.

The administration of COCs may influence human metabolism[30], affecting lipid and glucose profiles and thus inducing dyslipidemia and increased BMI[31]. In addition, they may expose to deficiency of several micronutrients, whose depletion is associated with obesity[32,33]. Dakshinamurti described for the first time the involvement of biotin in glucose metabolism[123]. In this study biotin-deficient rats exhibited a glucose profile more similar to a diabetic condition compared to non-deficient rats, as indicated by higher glucose tolerance test curves, as well as glucose phosphorylation and incorporation into glycogen in liver[123]. Subsequently they demonstrated that the effects of biotin are mediated by transcriptional activity, indicating a role on gene expression[124]. In light of this, biotin deficiency correlates to impaired oral glucose tolerance tests and decreased utilization of glucose in rats[123,125]. Clinical studies revealed that diabetic patients exhibited lower serum levels of biotin than controls with an inverse correlation between serum biotin and fasting blood glucose concentration[126,127]. Concomitantly, pharmacological doses of biotin improved diabetic state and they also decreased plasma lipid concentrations, influencing lipid metabolism.

Additional studies reported the relationship between biotin and lipid metabolism[128-130]. Rats genetically prone to develop elevated blood lipids display aspects of biotin deficiency as an inverse association between plasma lipids and biotin status[131]. A study[130] on healthy volunteers confirmed negative correlation between biotin levels and total plasma lipids also in humans. Overall, biotin supplementation can reduce plasma lipid concentration, suggesting its importance in glucose and lipid homeostasis[132].

Vitamin E

The term vitamin E describes a group of lipophilic antioxidant compounds that include four tocopherols and four tocotrienols indicated as α-, β-, γ-, and δ-[133]. Food sources of vitamin E are vegetables and fruits, oils and margarines, grains, nuts, seeds and fortified cereals. *In vivo*, vitamin E is constantly regenerated from ancillary antioxidants like vitamin C, whose levels influence local content of vitamin E.

Evans demonstrated that vitamin E plays also a key role in reproductive functions, as it prevents loss of spermatogenesis in males and the failure to retain zygotes in female rats[134].

Most importantly, vitamin E prevents propagation of free radicals in tissues acting as peroxyl radical scavenger. Being a family of fat-soluble compounds, it is incorporated into cell membranes and it contributes to their protection from oxidative damage[135].

Notably, COCs lead also to a deficiency of vitamin E. OC users indeed exhibit increased oxidative stress, especially in terms of lipid peroxidation, which is related to lower circulating levels of vitamin E[136-138]. Preclinical studies in rats revealed that the administration of contraceptive steroids significantly reduced plasma levels of tocopherol and increased dietary requirements of vitamin E[139]. In line with these results, a clinical study demonstrated that COCs reduce plasma tocopherols also in healthy Caucasian women, thus suggesting the need of dietary supplementation of vitamin E.

Furthermore, as vitamin E positively regulates cytosolic phospholipase A2 and cyclooxygenase (two rate-limiting enzymes involved in the arachidonic acid pathway), it enhances, in a dose-dependent manner, the release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation[140]. Renaud et al[141] found that OC users exhibit an increased blood-clotting activity, which may derive from reduced levels of α-tocopherol found in these subjects. Vitamin E supplementation can recover this alteration, reducing platelet overactivity[50].

Vitamin C

Vitamin C is a water-soluble vitamin, also known as ascorbate or ascorbic acid, which acts as cofactor in several metabolic reactions, including synthesis of collagen, carnitine and catecholamine, as well as in peptide amidation and tyrosine metabolism[10]. Deficiency of vitamin C may lead to serious clinical alterations like scurvy, poor wound healing, and connective tissue disorders.

Previous studies demonstrated that therapies based on COCs influence vitamin C status, as reported by reduced amount of ascorbate in plasma leukocytes, platelets, and whole blood entities. In particular, the use of OCs, specifically those con-

taining estrogens, correlates with lower levels of vitamin C, due to the increased rate of its metabolism[55,57,142,143]. Such effect is enhanced especially in those patients who have poor diet, unhealthy habits, or a pathology of malabsorption. In line with this, evidence in literature demonstrated that adequate dietary intake of ascorbic acid can counteract depletion induced by the use of OCs over a period that spans from 6 months to 7 years[144].

Vitamin C further exhibits positive effect on vaginal discharge, a common sign of local infections and frequently reported during therapies with COCs. Petersen et al[145] demonstrated the efficacy and safety of vitamin C in patients suffering from non-specific vaginitis with a randomized, double-blind, placebo-controlled study.

Moreover, vitamin C plays a central antioxidant role, acting as scavenger of free radicals and maintaining metal ions (e.g., iron and copper) in their reduced forms. Increased oxidative stress and lipid peroxidation can become a potential risk for cardiovascular diseases. Evidence indicated an increase of antioxidant enzymes, including catalase and glutathione peroxidase in women taking OCs compared to baseline levels, suggesting increased oxidative damage. Another study conducted on 120 healthy women taking OCs, demonstrated that a 4-week supplementation of vitamin C reduces the activities of peroxidase and reductase compared to a control group, confirming the beneficial role of vitamin C in counteracting oxidative stress during COC therapy[137].

Vitamin D

The term vitamin D refers to a group of fat-soluble steroid compounds, among which vitamin D2 and vitamin D3 are the major forms. The latter is often reported as the most effective one, probably due to a higher affinity for vitamin D binding protein that reduces its clearance, providing longer lasting concentrations in blood with respect to vitamin D2[146,147].

Vitamin D, specifically its active form 1,25-dihydroxy-vitamin D3, plays crucial roles in calcium homeostasis, bone metabolism, and cell differentiation and proliferation. Most of the reported activities are mediated by nuclear vitamin D receptor[148,149], which is expressed in tissues like intestine, skeleton and parathyroid gland as well as ovary and testis[150].

Levels of vitamin D are related to bone mineral density (BMD) homeostasis, which starts to decrease in women after 30 years of age depending on genetics, nutrition and lifestyle factors[151]. Bone mineral content changes across life cycle and increases during growth, accruing from 8 to 30 years of age. At this time, bone mineral content reaches a plateau, identified as a peak bone mass in young adulthood, and then gradually decreases in older age[152]. Several factors, including the onset of menopause and related hormonal disequilibrium with reduced estrogen levels, cause a gradual decline of BMD, resulting in decreased bone strength and density associated with increased fracture risk[153,154].

Considering its central role in calcium absorption and bone mineralization, positively associated with BMD, dietary supplementation with vitamin D is essential for minimizing the risk of bone damages. Studies demonstrated that administration of vitamin D, alone or in combination with calcium, exhibits significant beneficial effects on BMD[155-157]. More recent evidence also revealed that vitamin D in its active form modulates estrogen synthesis in ovarian granulosa cells[158].

Overall, since peak bone mass is physiologically attained by the third decade of life, dietary supplementation of vitamin D in women over 30 years of age may improve BMD and calcium homeostasis preserving bone health.

Magnesium

Mineral status appears frequently affected in women taking hormonal therapies, especially for what concerns magnesium, zinc and selenium levels. Magnesium is an essential element in biological systems[159], serving as cofactor in more than 300 enzymatic reactions[160]. Physiologically it plays a central role in stabilizing all the polyphosphate compounds in cells and it is crucial to make ATP biologically active.

Magnesium is also essential for regulating muscle contraction, blood pressure, insulin metabolism, and it is pivotal for the synthesis of DNA, RNA, and proteins[161]. In the nervous system, magnesium optimizes nerve transmission and neuromuscular coordination, and it protects neurons against excitotoxicity (excessive excitation leading to cell death).

Inadequate food intake of magnesium or the use of diuretics can lead to deficiency and serious consequences that include cardiovascular diseases, diabetes, anxiety disorders, migraines, osteoporosis[159,162].

Poor magnesium levels are common among women taking COCs[163-167], contributing to the onset of pathological conditions like anxiety and depression[168-170]. Tarleton et al[171] found a significant association between very low magnesium intake and depression phenomena, especially in younger adults. In

addition, reduced levels of magnesium, along with low levels of vitamins B2 and B6, correlate with the onset of other common adverse effects, including migraines and fatigue[172,173]. Magnesium is involved in mitochondrial production and ATP metabolism, and a reduced mitochondrial metabolism is an etiological factor of migraine[174]. Previous research reported lower levels of magnesium in serum, saliva and cerebrospinal fluid of individuals during and between migraine attacks[92,175-177]. Current evidence revealed that about 50% of patients with recurrent episodes of migraine exhibit low serum levels of magnesium[178]. In line with this, magnesium supplementation proved to reduce the frequency of attacks and the pain during acute migraine episodes[179]. Specifically, magnesium seems to block glutamatergic N-methyl-D-aspartate (NMDA) receptor, which actively contributes to pain transmission and to the wave of cortical spreading depression[160].

Many studies[163-167] confirmed lower serum magnesium levels in OC users compared to both non-users and women taking other forms of contraception. A similar outcome is consequence of the prophylactic treatment of postmenopausal osteoporosis based on estrogens and calcium. The resulting altered calcium/magnesium ratio influences processes of blood coagulation[159,180], increasing the risk of venous thrombosis, as described in a meta-analysis of 26 observational studies[181].

In addition, researchers demonstrated that magnesium supplements improve depressive symptoms in patients with chronic fatigue syndrome or premenstrual syndrome[182]. A recent work by Noah et al[28] suggests that magnesium supplementation may improve mood, anxiety, stress and overall, QoL.

Zinc

Zinc is another essential mineral with important biological functions. It plays a central role as cofactor for approximately 300 enzymes contributing to various processes, such as RNA and DNA metabolism, signal transduction and gene expression[183]. High levels of zinc are present in tissues like muscle, bones, kidney, liver, prostate, parts of the eye and semen[184]. Zinc is also stored in brain in specific synaptic vesicles by glutamatergic neuron, where it plays a key role in synaptic plasticity and learning processes[185].

The relation between zinc status and women taking OCs was described in 1968, when researchers observed that women taking OCs exhibited lower levels of zinc than non-users[56,186]. Following studies confirmed these data[6,8,187,188], suggesting that lower zinc serum levels could reflect a reduction of zinc status in tissues due to changes in zinc absorption, excretion or tissue turnover[187].

Various studies both in human and animals revealed that zinc deficiency can correlate to depressive symptoms[189-191]. Several works confirmed the observation of Hansen et al[192] in 1983 who first reported the potential role of zinc as marker in pathophysiology of depression. Studies demonstrated the effectiveness of zinc supplementation on psychological aspects, improving mood and QoL. Rats fed with a diet low in zinc exhibit more depressive symptoms than those fed with a normal diet[191]. Interestingly, clinical trials with depressed individuals revealed beneficial effects of treatments with antidepressants and zinc, compared to those with antidepressants alone[193,194].

In addition, zinc deficiency can be related to other adverse reactions occurring during OC treatments, such as hair dryness[195,196] or alopecia[197]. Scientific evidence indicates that zinc supplementation positively influences hair loss and dryness[198], which commonly occur during hormonal therapies.

Selenium

Selenium is an essential trace element abundant in meat and legumes, but also contained in fruits and vegetables[199]. Selenium is crucial for the functioning of several proteins, called selenoproteins, involved in the antioxidant response within brain and nervous system[200-202]. Furthermore, selenium contributes to maintain physiological turnover of neurotransmitters, preventing the occurrence of negative mood states[203]. Indeed, deficiency of selenium is related to the onset of depression, anxiety and confusion[201,204,205]. In low selenium intake conditions, brain receives a priority supply to prevent alteration in the turnover of several neurotransmitters. A study on rodent models reported an association between selenium deficiency and decreased concentrations of Brain Derived Neurotrophic Factor[206], which is associated with pathophysiology of major depressive disorder[207,208].

Several studies highlighted that OCs may interfere with selenium absorption and cause deficiency. A clinical study on 200 young women demonstrated that the administration of low-dosage OCs for a minimum of 3 months induce a statistically significant reduction in mean serum selenium levels compared to control subjects[187,209].

Selenium also plays a major role in thyroid functionality and in biosynthesis of thyroid hormones,

which regulate metabolism of the whole body. Clinicians and researchers agree on the evidence that some neuropsychiatric manifestations, such as mood disorders, cognitive dysfunction and depression, may be related to altered thyroid functionality[210,211]. Indeed, a US study[212] revealed that high dietary selenium intake or supplementation may improve mood in terms of reduced subscores of anxiety, confusion and total mood disturbance.

In addition, selenium deficiency can increase the risk of cardiovascular diseases. In this regard, Nève[213] demonstrated the beneficial effect of selenium on cardiovascular diseases due to the scavenging activity of glutathione peroxidase, which prevents modifications of lipids and reduces platelet aggregation.

Conclusions

COCs are among the most used drugs worldwide, even if the occurrence of adverse effects – or the fear of them – may negatively influence patients' compliance and QoL. Such effects include both physical changes, such as water retention, increased body weight, cellulite, leg swelling, vaginal discharge or hair dryness, and psychological alterations due to low self-esteem and non-objective self-perception.

As reported by WHO, the combined estrogen/progestogen therapy exposes women to several side reactions related to lower levels of specific vitamins and minerals, including vitamins B, C and E, zinc, magnesium, and selenium. Evidence in literature confirmed that reduced levels of such micronutrients may negatively influence general health by inducing the above-mentioned adverse effects.

Several preclinical and clinical studies reveal that the administration of these vitamins and minerals is effective for addressing nutritional needs of women and for recovering adverse conditions (Table I).

Of course, further prospective and randomized clinical trials would be encouraged for imple-

Table I. Micronutrient supplementation and adverse effects of COCs.

Micronutrients	Targeted adverse effects
Centella Asiatica extract	Fluid retention
	Cellulite
	Edema
	Leg swelling
	Depressive and anxious symptoms
Vitamin B9 (Folate)	Hyperhomocysteinemia
	Thromboembolism
	Neural tube defects
Vitamin B12 (Cobalamin)	Hyperhomocysteinemia
	Thromboembolism
	Migraine attacks
Vitamin B2 (Riboflavin)	Migraine attacks
Vitamin B6 (Pyridoxine)	Depressive symptoms
	Headache and dizziness
	Breast tenderness
	Thromboembolism
Vitamin B8 (Biotin)	Dyslipidemia and increased BMI
	Glucose tolerance levels
Vitamin E	Breast tenderness
	Thromboembolism and platelet overactivity
	Oxidative stress
Vitamin C	Vaginal discharge
	Non-specific vaginitis
	Oxidative stress
Vitamin D	Calcium homeostasis and bone health
Magnesium	Migraine attacks
	Thromboembolism
	Depressive and anxious symptoms
Zinc	Hair dryness and alopecia
	Depressive and anxious symptoms
Selenium	Oxidative stress
	Depressive and anxious symptoms

*Highlights on micronutrients and targeted side reactions occurring during COC treatment.

menting the use of dietary supplements in women using COCs. However, a combined supplementation of all these micronutrients, acting on different aspects and pathways, may prevent and counteract discomforts and side effects related to COC-based treatments, improving safety, tolerability and patients' compliance to the therapy.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethics Approval

Not applicable.

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