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Review Article

## Vitamin and mineral needs during the oral contraceptive therapy: a systematic review

Giulia Dante<sup>1</sup>, Alberto Vaiarelli<sup>2</sup>, Fabio Facchinetti<sup>1\*</sup>

<sup>1</sup>Department of Mother-Infant, University of Modena and Reggio Emilia, Italy

<sup>2</sup>Department of Reproductive Medicine, Policlinico Universitario di Messina, Messina, Italy

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**\*Correspondence:**

Dr. Fabio Facchinetti,

E-mail: facchi@unimore.it

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### ABSTRACT

**Objectives:** There is growing evidence that women using OCs change in serum trace elements and vitamins. Nowadays, in many cases, side effects associated with low levels of micronutrients are not considered during oral contraceptives (OCs) therapy. This review aims at checking the present literature in order to verify the evidences. Our purpose is to underline this aspect contributing to improve the therapeutic approach with OCs.

**Methods:** Systematic literature search was performed in electronic databases, covering the period from January 1967 to January 2012.

**Results:** Ninety-five articles were located; a cross sectional randomized and three RCTs studies were considered eligible.

**Conclusions:** A decrease in the serum concentrations of zinc, selenium, phosphorus and magnesium have been reported in OC users. Such reductions were proportional to the duration of contraceptive use. These reductions may imply a reduction in the probability of having a pregnancy and/or an increase of serious illness for the unborn. In this regard, a supplementation with the above compounds could be useful in OC users, namely for reducing side effects.

**Keywords:** Oral contraceptive pill, Nutritional requirements, Vitamins deficiency, Micronutrients deficiency, Serum trace elements

### INTRODUCTION

In recent years there has been growing interest concerning alterations of metabolic processes and trace element profiles associated with the use of oral contraceptives (OC). Such changes are driven by genetic predisposition as well as environmental factors, changes in lifestyle, dietary habits and active ingredients of hormonal compounds. Indeed, several reviews indicate that OC administration affects metabolism of vitamins and minerals.<sup>1-5</sup>

Some of these micronutrients are co-factors and/or coenzymes involved in important metabolic pathways. Changes in their tissue level or bioavailability might play

a significant role in health risk and might be involved in the pathogenesis of some disorders.<sup>6</sup>

Literature data report the administration of various combined estrogen-progestin pills is able to change micronutrient levels. Unfortunately, it is not always clear which component of the OC is responsible for the observed changes. Even nutritional experts' opinions differ in the interpretation of the biochemical results and the uncontrolled administration of dietary supplements to OC users makes comprehension of the effects on the women's health more difficult.<sup>7,8</sup>

The present systematic review aims at providing a comprehensive view of the literature evidence about the changes of nutritional needs in women who use OCs.

## MATERIALS AND METHODS

Systematic literature searches were performed in April 2012 using the following electronic databases: Medline, Amed and The Cochrane Library. We performed a search over the period from January 1967 to January 2012; a cross sectional randomized and three RCTs studies were included.

The search terms were: ‘oral contraceptives’, ‘homocysteine’, ‘micronutrients’, ‘serum trace elements’, ‘vitamins’, ‘minerals’, ‘vitamin A’, ‘vitamin E’, ‘vitamin C’, ‘vitamin B<sub>6</sub>’, ‘vitamin B<sub>12</sub>’, ‘iron’, ‘copper’, ‘zinc’, ‘selenium’, ‘magnesium’, ‘calcium’, ‘folic acid’, ‘folate status’.

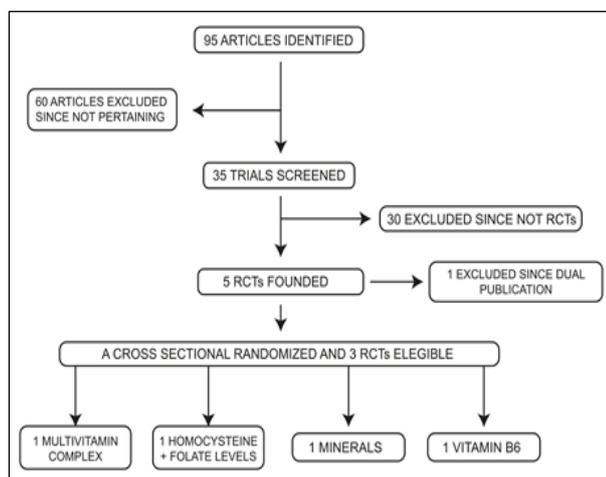
The search was limited to articles published in English and easily retrievable via the home library.

Further relevant papers were located by hand-searching the reference lists of recent trials. We attempted to obtain hard copies of all the papers listed through our own university library or by interlibrary loans. Only human studies were included while *in vitro* investigations were excluded.

This systematic review was written based on the Quorum Statement guidelines.<sup>9</sup>

## RESULTS

Decision tree is reported in Figure 1.



**Figure 1: Schematic representation of studies considered.**

Out of the 95 studies that were identified, 60 were excluded because they did not evaluate vitamin or mineral changes in OC users.

The remnant 35 studies were screened, 30 of them being excluded because they were not designed as RCTs while 1 was a duplicate publication. This process allowed a

cross sectional randomized and 3 RCTs studies which were eligible for this review.<sup>10-13</sup>

Two of them pertain the effects of either a daily multivitamin complex<sup>10</sup> or a vitamin B6 supplement<sup>13</sup> on the reduction of OC side effects. Two other trials evaluated the effects of OC use on either serum trace elements, calcium and phosphorus levels<sup>11</sup> or on the folate status and homocysteine levels.<sup>12</sup>

Inclusion and exclusion criteria as well the main outcome measures for all those studies are described in Table 1.

The study of Bart et al.<sup>12</sup> was a randomized double blind trial which investigated the change of folate in red blood cells (RBC) and plasma, and homocysteine levels during a 24-week oral administration of ethinyl estradiol (EE) 20 mcg/drsp 3 mg/levomefolate calcium 0.451 mg compared with an established OC containing EE 20 mcg/drsp 3 mg. For each 28-day treatment cycle, healthy women seeking contraception received EE/drsp/levomefolate calcium for 24 days followed by levomefolate calcium 0.451 mg alone for 4 days or EE/drsp for 24 days followed by placebo for 4 days. Compliance was good in both groups.

Three hundred seventy-nine women were randomized (EE/drsp/levomefolate calcium, N=285; EE/drsp, N=94) and received at least one dose of study treatment. During the study there was a drop out of 100 women who prematurely left the treatment. However, assessment of the outcomes was performed with both per protocol set (PPS) and full-analysis set (FAS).

Primary outcome of the study was the evaluation of RBC folate and plasma folate levels at week 24. Mean RBC folate levels in PPS increased from  $990 \pm 390$  nmol/L to  $1406 \pm 440$  nmol/L at week 24 in subjects who received EE/drsp/levomefolate calcium while no particular changes were observed in the EE/drsp group. Similarly, a statistically significant increase between baseline and week 24 was observed for plasma folate in EE/drsp/levomefolate calcium group, whereas only a small variation was observed with the EE/drsp. Within the FAS, both treatment groups provided RBC and plasma folate levels comparable to those of the PPS at baseline and at week 24.

Secondary outcomes were RBC folate and plasma folate at weeks 4, 8, 12, 16 and 20, plasma homocysteine levels at weeks 4, 8, 12, 16, 20 and 24 and evaluation of NTD risk reduction based on the changes of RBC folate levels.

Within the PPS, subjects who received the EE/drsp/levomefolate calcium reported an increase of RBC folate levels at all time points. Furthermore, after 4 weeks of EE/drsp/levomefolate calcium treatment, plasma homocysteine levels decreased to  $6.9 \pm 1.1$  mcg/L at week 8, while no reduction was observed in the EE/drsp group. Similar results were obtained within the FAS.

**Table 1: Features of randomized controlled trials.**

Ref.	Study design	Treatment/ Dose Duration	N° of subjects	Inclusion criteria	Exclusion criteria	Assessment of the response	Results
(11)	Cross-sectional randomized	Different hormonal contraceptives for at least 12 months	N°= 100 Treatment: - OC: 50 - injectables: 25 - IUD: 25 Controls: 50 age-matched non contraceptive users	Women aged 18-40 years, on different OC for at least 12 months	Pregnancy or lactation	Serum was analysed using atomic absorption spectrophotometer for zinc, copper, manganese, iron, selenium, cadmium, lead and magnesium while colorimetric method was used for phosphorus and calcium. BMI was calculated as weight in kg/h in meter squared.	The mean serum Zn, Se, P, Mg, levels obtained from subjects on contraceptives were significantly lower than those of the control group. The mean serum Cu, Fe, Ca and Cd levels were significantly higher in participants on contraceptive when compared with the control group. Mn and Pb levels were similar in participants and control groups.
(13)	Randomized, triple-blinded, controlled	30 µg norgestrel and 30 µg EE + 150mg vitamin B <sub>6</sub>  30 µg norgestrel and 30 µg ethinyl estradiol + placebo  30 days	N°=124  Treatment:62  Placebo:62	Women aged 18-40, in good general health; previous users or new acceptors of OC, with symptoms, such as nausea, headache, vomiting, dizziness, depression, and/or irritability, not explained by any specific pathology and likely to be OC side effects.	Contraindications for steroidal contraceptive use; the use of prescribed medications to treat OC side effects; and having a pre-existing neuropathy or other symptoms that could be confused with possible vitamin B <sub>6</sub> toxicity.	Severity of nausea, headache, vomiting, dizziness, depression, and irritability measured in a quantitative scale.	From admission to follow-up, there was a decrease in the severity of all symptoms in both groups. There was no statistically significant difference in the reductions found in the vitamin B <sub>6</sub> , and the placebo groups, although reductions in the severity of headache and dizziness were greater in the B <sub>6</sub> group.

(12)	Randomized, double-blind, active-controlled, parallel-group	EE/drsp+levomefolate calcium: 20mcg/3mg/0.451mg  EE/drsp+placebo: 20mcg/3mg  24 weeks	N°=572  Treatment:285  Placebo:94	Healthy female volunteers aged 18–40 years requesting OC . Normal or non-suspicious cervical smear at screening or within 6 months prior to screening..	Pregnancy, lactation, abortion; BMI>35; hypersensitivity to any of the study drug ingredients; any disease or condition that could compromise the function of body systems or affect the pharmacokinetics of the study medication; current or history of clinically significant depression, alcohol or drug abuse; treatment with prohibited concomitant medications; less than 6 menstrual cycles since intramuscular depot contraception at screening visit; less than one menstrual cycle since removal of hormone containing implants at screening visit; expected major surgery or prolonged immobility during the study period.	RBC and plasma folate levels	Increases in mean RBC and plasma folate levels were observed in women who received EE/drsp/levomefolate calcium. Marginal fluctuations were observed with EE/drsp.
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(10)	4-cell randomized, blind	Norethindrone+EE 1 mg/0.035 mg + Daily multi-vitamin*					
		Norethindrone+EE 1 mg/0.035 mg + Placebo	N° OC+vitamins= 1288	Not described	Not described	Methodology of Potter *	Despite no substantial differences, most of the side effects in the multi-vitamin group were decreased
		Norethindrone+EE 0.5 mg/0.035mg + Daily multi-vitamin**	N° OC+placebo= 1363				
		Norethindrone+EE 0.5 mg/0.035mg + Placebo					
12 months							

OC: oral contraceptives; EE: Ethinyl Estradiol; IUD: uterine device; BMI: body mass index; Zn: zinc; Cu: copper; Mn: manganese, Fe: iron; Se: selenium; Cd: cadmium; Pb: lead; Mg: magnesium; P: phosphorus; Ca: calcium, RBC: red blood cells; Kg: kilogram; h: height.

\* = Potter R.G., in *Family Planning in Taiwan* (R. Freedman and J.Y. Takeshita, eds.) Princeton University Press, Princeton, 1969; 458-483

\*\* = 1.4 mg of vitamin B<sub>1</sub>, 1.7 mg of vitamin B<sub>2</sub>, 10 mg of vitamin B<sub>6</sub>, 4 mcg of vitamin B<sub>12</sub>, 0.8 mg of folate, 60 mg of vitamin C and 16 mg of niacin.

In addition, using the Daly model,<sup>14</sup> NTDs risk reduction defined as a decrement in RBD folate levels from baseline to week 24 was evaluated as secondary variable. In the EE/drsp/levomefolate calcium group, a mean NTD risk reduction of 0.51 per 1000 births (corresponding to an estimated mean relative risk reduction of 37%) was calculated compared to a mean of 0.03 per 1000 births in the EE/drsp group.

Incidence and drop out due to adverse reactions were similar for both groups: upper respiratory tract infections and low-density lipoprotein increase were the most frequently reported events.

The study of Villegas et al.<sup>13</sup> was a randomized, triple-blinded controlled trial, conducted to evaluate the effects

of vitamin B<sub>6</sub> on the severity of the side effects of a low-dose combined OC (30 µg norgestrel and 30 µg EE).

A total of 124 women were enrolled into the study and divided in two treatment groups (OC plus vitamin B<sub>6</sub> and OC plus placebo). The treatment was performed for 30 days. The baseline characteristics between the two groups were similar except for headache: a higher proportion of women in placebo group reported moderate to severe headache at admission than in the vitamin B<sub>6</sub> group (p <0.05).

From enrolment to the follow-up visits (1-3 months), severity of side effects was measured using a quantitative scale ranging 0 to 3. Women in the vitamin B<sub>6</sub> group reported a decreased severity of the OC side effects,

mainly headache and dizziness, compared to the placebo group, despite no statistically difference was reported.

The study of Sriani<sup>10</sup> was a 4-cell randomized trial versus placebo conducted in 3 diverse sites in Sri Lanka to evaluate the impact of daily vitamin supplement, in preventing OC side effects.

The composition of the vitamin complex was: 1.4 mg of vitamin B<sub>1</sub>, 1.7 mg of vitamin B<sub>2</sub>, 10 mg of vitamin B<sub>6</sub>, 4mcg of vitamin B<sub>12</sub>, 0.8 mg of folate, 60 mg of vitamin C and 16 mg of niacin.

The OC used were: norethindrone-EE (1 mg/0.035 mg) plus daily multi-vitamin or placebo, norethindrone-EE (0.5 mg/0.035 mg) plus daily multi-vitamin or placebo.

The trial was conducted in 3 diverse sites: an urban area and two different rural areas. The first follow-up was scheduled 1 month after admission to the study. Further assessments were scheduled at 2-3 month intervals for 12 months.

Results demonstrated that in the urban area there was a lower frequency of most side effects, but this trend was not consistent and in most cases not statistically significant. No significant differences were found in the rural areas. Despite no substantial differences, most of the side effects in the multi-vitamin group were decreased.

Only one RCT focused on serum trace elements.<sup>11</sup> In this cross-sectional randomized trial, Akinloye et al. performed a study analysing blood samples collected from 150 women of child-bearing age. One hundred of them were on different contraceptive methods (50 OC, 25 injectable and 25 intra-uterine device). Fifty non-contraceptive users served as control.

Serum zinc, copper, manganese, iron, selenium, cadmium, phosphorus, calcium, lead and magnesium levels were analysed. Except manganese and lead, results showed a significant difference between OC users and controls of all the above mentioned trace elements.

In addition, OC group was separately compared with injectable and intra uterine device (IUD) users, while women on injectables were compared with intra-uterine device users.

Iron levels showed significant differences in all comparison groups. On the contrary, no significant differences have been reported on manganese and lead levels.

Cadmium levels showed a significant difference only in control versus IUD group.

Copper showed significant differences in all the groups except in OC versus injectables and similarly, magnesium levels did not show significant difference only in the control group versus injectables.

Zinc and selenium levels showed significant difference between all the groups but no significant difference was reported between the IUD users versus control and the OC users versus injectables.

Finally, calcium and phosphorus levels move on opposite directions, with an increase of serum calcium levels and a decrease of serum phosphorus levels in women on contraceptives.

The comparative difference of all the analysed data is resumed in Table 2.

**Table 2: Comparative differences between contraceptive users groups, and between contraceptive and control groups, using Student “t” test (p values set at p<0.05).**

Parameter	Contraceptive vs. control	Control vs. OC	Control vs. injectables	Control vs. IUD	OC vs. injectables	OC vs. IUD	Injectables vs. IUD
Zinc	↓ 0.001	0.000	0.000	NS	NS	0.000	0.000
Copper	↑ 0.001	0.000	0.000	0.000	NS	0.000	0.000
Manganese	NS	NS	NS	NS	NS	NS	NS
Iron	↑ 0.001	0.000	0.000	0.000	0.000	0.000	0.000
Selenium	↓ 0.001	0.000	0.000	NS	NS	0.000	0.000
Cadmium	↑ 0.05	NS	NS	0.002	NS	NS	NS
Phosphorus	↓ 0.001	0.000	NS	NS	0.000	0.000	NS
Calcium	↑ 0.001	0.000	NS	NS	0.000	0.000	NS
Lead	NS	NS	NS	NS	NS	NS	NS
Magnesium	↓ 0.001	0.000	NS	0.003	0.000	0.000	0.022

Adapted by Akinloye et al.<sup>11</sup>  
 NS= not significant  
 ↑ = increment  
 ↓ = reduction

## DISCUSSION

Despite a relatively high number of reports concerning the effects of OC on metabolic processes and serum trace element profiles, only a few of them had been designed as RCTs.

This review analyzed three placebo-controlled trials that described the effects of different supplements associated with OC use.<sup>10,12,13</sup> In some of them<sup>13</sup> dietary supplements reduced adverse symptoms correlated with OC, namely as headache and dizziness. One trial<sup>12</sup> reported an improvement of RBC and plasma folate levels associated with vitamin supplements. Finally, another trial<sup>11</sup> reported a decrease in the serum concentration of zinc, selenium, phosphorus and magnesium selectively in OC users.

Our systematic review has some limitations, i.e. the different outcomes are reported with different statistical approach and they cannot be summarized in a meta-analysis. This reduces the possibility that conclusion reached in the single trial could be widespread. Nevertheless, bearing the above limitations in mind, this survey allows some considerations.

### **Folate status**

Folate deficiency has been associated with a number of clinical conditions, including neural tube defects (NTDs),<sup>15</sup> a leading cause of morbidity and mortality in neonates.<sup>16</sup> Currently, folic acid supplementation guidelines issued by the US Preventative Services Task Force recommend all women of childbearing age a daily supplementation of 0.400–0.800 mg of folic acid. In particular, this supplementation has to be commenced at least one month before conception and continued during the first two-three months of pregnancy.<sup>17</sup>

Early observational studies in OC users conducted in the 1960s led to the hypothesis that the use of synthetic hormones may negatively influence folate status.<sup>18,19</sup> Subsequently, multiple studies on healthy women were performed: in all these cases, the dietary intake has been judged from adequate to good.<sup>7, 20-22</sup>

Some Authors suggested that the absorption of naturally-occurring food folate may be impaired in women using OC.<sup>23</sup> It was further reported that absorption of the polyglutamyl folate form is reduced by about 50% in OC users versus non-users with no differences detected in the absorption of monoglutamyl folate. It was hypothesized that OC may impair the enzymatic cleavage by the intestinal folate conjugated enzyme required for polyglutamyl folate absorption. An additional proposed mechanism for impaired folate status is that OC may increase the clearance of folate from blood,<sup>24</sup> possibly as a result of changes in liver enzymes or renal folate-binding proteins involved in reabsorption in the kidney.<sup>25</sup>

Other investigators proposed that OC use may impair folate metabolism via increased activity of microsomal enzymes requiring folate. In addition, there have been several early reports of increased serum,<sup>26</sup> and leukocyte folate binders in OC users.<sup>27,28</sup> It should be considered that the hormonal content of OCs was much higher in the 1960s and 1970s when these studies were carried out, raising the question of whether conclusions regarding the effect of OC use on folate status can still be extrapolated.

Anyway, the results obtained from the RCT included in this review<sup>12</sup> confirm the findings of previous trials reporting that the levomefolate calcium intake increases both RBC and plasma folate levels.<sup>29</sup> Furthermore, since it is recognized that only approximately 20%<sup>4</sup> of women in reproductive age consume the recommended intake of folic acid to reduce NTD risk, it will be important to plan supplementation in categories of women at higher risk such as OC users.

However, the decreases in the prevalence of NTDs have been reported since folic acid fortification of United States grain products began. It is not known whether folic acid plays a role in reducing the severity of occurring NTDs. Kirk et al. have carried out a study in which show that infants with spina bifida experienced a significantly improved first-year survival rate of 92.1% during the period of mandatory folic acid fortification. Infants with encephalocele had a statistically non-significant increase in survival rates, i.e., 79.1% with folic acid fortification, compared with 75.7% for earlier births. Folic acid may play a role in reducing the severity of NTDs in addition to preventing the occurrence of NTDs. This phenomenon contributes to our understanding of the efficacy of folic acid.<sup>30</sup>

### **Vitamin B<sub>6</sub>**

Vitamin B<sub>6</sub> is an essential micronutrient required in coenzyme form (pyridoxal 5'-phosphate, PLP) for over 100 enzymes involved in amino acid, lipid, and glucose metabolism.

Vitamin B<sub>6</sub> deficiency has been associated with a number of clinical symptoms, including convulsions, abnormal electroencephalograms,<sup>31,32</sup> and may compromise health of the mother increasing the risk of complications during pregnancy.<sup>33</sup>

The use of vitamin B<sub>6</sub> has been recommended as a treatment for morning sickness in early pregnancy as well as for the management of women with Premenstrual Syndrome.<sup>8</sup> Uncontrolled studies reported that a 25-30 mg daily supplementation of vitamin B<sub>6</sub> can reduce the incidence of side effects among OC users.<sup>34</sup>

The association between vitamin B<sub>6</sub> status and OC use was first made during the '60s<sup>35</sup> when increased urinary excretion of xanthurenic acid, kynurenine, and 3-OH-

kynurenine was observed following a tryptophan load test. Several studies confirmed the finding of abnormal tryptophan metabolism in women using OCs, as well as its correction with mega doses of pyridoxine hydrochloride.<sup>36,37</sup> There is general consensus that estrogen disrupts tryptophan metabolism independently from vitamin B<sub>6</sub> status, making the tryptophan load test a poor indicator of vitamin B<sub>6</sub> status in OC users.

In a recent study performed in the United States<sup>38</sup> plasma PLP concentration was found to be significantly reduced in 75% of low-dose OC users suggesting that higher intakes may be necessary to maintain adequate vitamin B<sub>6</sub> status. These findings corroborate the previously reported data in which abnormalities of tryptophan metabolism in OC users were corrected by supplementation with mega-doses of vitamin B<sub>6</sub>.<sup>35,39</sup>

In the trial included in our systematic review<sup>13</sup> there was a non-significant although appreciable effect of vitamin B<sub>6</sub> supplementation on headache and dizziness related to OC use and higher proportions of women in the vitamin B<sub>6</sub> group reported decreased OC-related side effect severity compared to the placebo group. Based on this small evidence further trials should be performed in order to define if supplementation with pyridoxine can reduce the incidence of side effects among OC users.

### **Vitamin B<sub>12</sub>**

Vitamin B<sub>12</sub> (cobalamin) is an essential nutrient which acts as a cofactor for methionine synthase, accepting a methyl group from 5-methyltetrahydrofolate (5-Me-THF) in order to regenerate THF. As with inadequate maternal folate status, impaired maternal cobalamin status is an independent risk factor for NTDs.<sup>40</sup>

Methylmalonic acid (MMA) levels are often increased in early stages of vitamin B<sub>12</sub> deficiency, and Adams et al.<sup>40</sup> suggested that cobalamin status may be related to the development of NTDs after finding that women with mid-trimester serum MMA levels >90<sup>th</sup> percentile had a 13-fold higher risk for having an NTD affected pregnancy.

Lower serum cobalamin concentrations have been associated with OC use,<sup>41-43</sup> but the reduction in serum concentrations may not indicate a true cobalamin deficiency. This is supported by the lack of change in functional cobalamin indicators, such as homocysteine (Hcy) and MMA concentrations. Specifically, in some studies, no differences were detected in urinary MMA concentrations,<sup>44</sup> plasma MMA concentrations, or plasma Hcy concentrations with OC use compared to controls.<sup>43,45</sup>

However, in a study where dietary intake was controlled in addition to a number of other key variables, Riedel et al.<sup>42</sup> reported that low serum cobalamin concentrations were associated to OC use. In OC users, the median

concentrations of both serum cobalamin and plasma holotranscobalamin (holoTC) were approximately 25% lower than in controls. Neither plasma concentrations of MMA nor Hcy concentrations were significantly higher in OC users versus non-users, although OC administration increased the risk of having serum MMA concentrations in the highest quartile. In OC users, both serum cobalamin and holo-TC were inversely correlated with plasma MMA and Hcy, while no such relationships were found in non-OC users. Since the mean concentrations of MMA and Hcy were unaffected by OC use, the investigators suggested OC use may result in a redistribution of cobalamin rather than a depletion of intracellular cobalamin. A potential explanation for the differences between studies is the diverse EE content of OCs.

In the trial included in our review<sup>10</sup> findings show a negative influence of OC on the vitamin B<sub>12</sub> status. This small evidence supports the concept that vitamin supplements could be helpful in OC users although these findings are not easily transferred to other populations.

### **Serum trace elements**

Several studies have shown that in women under OC, concentrations of serum trace elements have been altered, although the magnitude of alteration is variable. Changes in the tissue level or bioavailability of such elements could play a significant role in health as well as in the pathogenesis of some disorder.<sup>1,46,47</sup>

Akinloye et al.<sup>11</sup> confirmed these data, reporting a significant reduction in the levels of some trace elements in women on different contraceptive methods, and especially in the OC users, when compared with non-OC users. In detail, a significant decrease in the serum concentration of zinc, selenium, phosphorus and magnesium was described while a significant increase in serum level for copper, iron, cadmium was observed.

A recent case-control study<sup>48</sup> was conducted to ascertain the influence of OC on serum zinc and selenium in OC users. The concentration of those elements was determined in 50 healthy women with normal menstrual cycles as a control group and 50 women taking low-dose OC for a minimum of 3 cycles. Use of OC resulted in a significant decrease mainly in serum zinc levels. These results were confirmed by the RCT analysed in this review.<sup>11</sup>

In the same trial,<sup>48</sup> a significant reduction in the serum phosphorus levels and a significant increase in the serum calcium levels in women on OC respect to women on injectable contraceptives was described. These data are confirmed in our RCT. These findings are correlated to the fact that calcium and phosphate move in opposite directions therefore significantly elevated serum calcium level is reciprocated by a significantly reduced serum inorganic phosphate level.

A significantly decreased in serum magnesium levels in OC users was found confirming the hypothesis that the OC play an important function in the absorption and metabolism of this element.<sup>49</sup>

Increased serum copper and iron levels were observed in particularly in women on IUD. The most likely hypothesis suggest that increased level of copper in contraceptives users may be related to a saturation of ceruloplasmin or in a plasma level reduction.<sup>2,50</sup> Also the increased levels of iron may be associated with the decreased menstrual blood flow which usually occurs in these subjects.<sup>51</sup> No significant variation is described about serum cadmium levels in OC users.

In conclusion, these findings demonstrated an alteration in the levels of some vitamins serum trace elements in women taking OCs. These effects worsen with long-term consumption. A supplementation with the above compounds could be useful in OC users, in order to reduce possible side effects.

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