PJN
ISSN 1680-5194

PAKISTAN JOURNAL OF NUTRITION

ANSInet
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
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Pakistan Journal of Nutrition 15 (8): 800-809, 2016
ISSN 1680-5194

The Nutritional Implications of Oral Contraceptives on Women

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Abstract: Oral contraceptives are used by a large proportion of women to prevent pregnancy and also for family planning purposes. This review focused on the effects of oral contraceptives on micronutrient (vitamins and minerals) status of users. Several studies have investigated whether or not women on oral contraceptives need different amounts of some vitamins and minerals. These studies have shown that the key nutrients affected by oral contraceptives include folic acid, vitamins B2, B6, B12, vitamin C, A and E and the minerals: iron, copper, magnesium, sodium, selenium and zinc. The levels of these micronutrients in the blood of women who use oral contraceptives compared to women who do not, have been the focus of most research. Taking appropriate dietary supplements is recommended to be the initial intervention approach by clinicians since several factors such as bioavailability, malabsorption, inadequate consumption, unhealthy lifestyles and pathological conditions can interfere more with the dietary sources of these micronutrients. Review on the food sources of the lacking nutrients and the dietary management of nutritional deficiencies were also documented in this review.

Key words: Oral contraceptives, micronutrients, nutrition status, vitamins, minerals

INTRODUCTION

Nutrient drug interaction following the administration of drugs could affect the body either positively or negatively (Galland, 2010). Studies have shown that drug nutrient interaction may lead to under-nutrition or over-nutrition depending on factors such as nutrient absorption, metabolism or utilization (British Nutrition Formula (BNF), 2009; Galland, 2010). Nutrition generally affect the bio-transformation of many drugs, however, a good knowledge pertaining to oral contraceptives is still scanty (Chivorn, 2014). Interaction involving nutrients and drugs as far as the pharmacokinetic and pharmacodynamics are concerned may be synergistic or antagonistic (WHO, 1975; Galland, 2010). There are limited studies on the interactions of oral contraceptives on the nutritional status of women (Chivorn, 2014).

Oral contraceptives are drugs that are prescribed by qualified health professional for the purpose of birth control and prevention of pregnancy in women (Anderson, 2010). When oral contraceptives are taken correctly, it helps to prevent ovulation and thus pregnancy. The female hormones such as the estrogen and progestin are the main constituents in oral contraceptives formulae that prevent ovulation (Anderson, 2010).

Hormones are powerful chemicals that alter several activities and can affect several parts of the body (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012). Studies have demonstrated that physiological and physical changes occur in women as a result of oral contraceptives use. These changes have been attributed to the increased levels of female hormones (Anderson, 2010). These changes may have an impact on the general health and nutritional wellbeing of the women (Mahan and Escott-Stump, 2008; Anderson, 2010; Mahan *et al*., 2012). Hormonal contraceptives for instance are noted to present some side effects that discourages majority of women from their use as a method of family planning. However as far as nutrition is concerned, questions that arise include; the what are the impact of oral contraceptives on nutrition status, do women on oral contraceptives require dietary supplements and what are the strategies to manage or prevent malnutrition attributable to the use of oral contraceptives in women (Mahan and Escott-Stump, 2008; Anderson, 2010; Mahan *et al*., 2012).

Studies have shown that both vitamins and minerals are affected by the use of oral contraceptives. Vitamins that are mostly affected as a result of oral contraceptives (birth control) pills are vitamin B6, vitamin B12, folic acid, riboflavin, vitamin C and vitamin A. While the minerals affected include iron, zinc, copper, sodium, selenium and magnesium (Anderson, 2010; Chivorn *et al*., 2014). Malnourished women on contraceptives may experience

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devastating effects as a result of micronutrient deficiencies and health status. Studies hitherto have been unable to resolve whether micronutrient supplementation may reduce such side effects (Chivorn *et al*., 2014). It was indicated that, women taking Vitamin B6 supplement while on oral contraceptives were less likely to experience side effects in a nutritionally vulnerable population (Chivorn *et al*., 2014).

However, the underlying health and nutritional status of these women should be further examined by health professionals and reproductive health policy makers in the context of providing contraceptive services. Micronutrient supplementation may largely be implicated in women who are on oral contraceptive to help replenish nutrients depletion and overall health and nutritional status of women; thus especially with vitamin B6, in reproductive-aged women using hormonal contraception should be conducted in other settings to determine the potential for widespread adoption (Chivorn *et al*., 2014). Family planning in contemporary times are largely linked with improved population level health outcomes, including decrease in maternal and neonatal mortality and improvements in overall health of women (Rutstein, 2005; Cleland *et al*., 2012; Chivron *et al*., 2014. However, some other studies have indicated that combined oral contraceptives (COCs) are the most popular of contemporary family planning methods with 15% coverage (Sedgh *et al*., 2007). There is little documented evidence about the severity of adverse side effects of the use of oral contraceptives and this phenomenon are expected to be different among populations in higher and lower income countries (Sedgh *et al*., 2007).

The convenience in the usage of oral contraceptives, its accessibility and cost have been suggested as reasons for their popularity, however, there are observed complications that prevent further increases in the adoption of oral contraceptives (Ministry of Health-Cambodia, 2011; Chivorn *et al*., 2014). Physical side effects appear to play an important role as barriers to the use of oral contraceptives in Cambodia and other Asian countries (Ministry of Health-Cambodia, 2011; Chivorn *et al*., 2014).

Data from Ministry of Health in Cambodia showed side effects as a critical issue in the uptake and continuation of family planning services. A 2005 survey of perceptions of available contraceptive methods among Cambodian women with unmet family planning needs showed that 70% of those who discontinued use of oral contraceptives, did so because of the observed side effects (Ministry of Health-Cambodia, 2011).

A drug is prescribed to produce specific, desired effects; however, it can also produce undesired adverse effects, including being harmless, hazardous or lethal. The goal of pharmacology is to optimize the benefits of a drug while minimizing its adverse effects. Nutrient-drug interactions are related to the dose and form of the drug, the condition or disease for which the drug is prescribed, the client's characteristics and the diet prescribed for the client. While we may not be able to eliminate adverse effects, they can often be managed. Nutrition education is one method that can be used to reduce the risk of negative effects associated with food-drug interactions (Chivron *et al*., 2014). There is however no conclusive evidence to indicate that women who take birth control pills need different amounts of vitamins and minerals to prevent nutritional deficiencies. However, what individual women needs, vary from one to another. Women on birth control pills should eat a well-balanced variety of foods that are good sources of vitamins and minerals (Anderson, 2010). It is a general principle of therapeutics to ensure the administration of low dose of a drug as possible, for as short a time as possible to minimize or eliminate adverse drug effect in the body, since it is observed that, increase in drugs and oral combination may lead to nutrient interaction (Galland, 2010). This review discussed the effects of oral contraceptives on nutritional status and the nutritional management of the various identified nutrients affected by the use of oral contraceptives.

Vitamins

Effects of oral contraceptives on vitamin A (retinol, retinal and retinoic acid) status: Studies have shown that retinol in the human body are elevated in the serum of about 30-80% of oral contraceptives users (Galland, 2010; Anderson, 2010). Beta-carotene levels are mostly unchanged or minimally reduced in these users (Anderson, 2010). The estrogen in the oral contraceptives have been implicated to cause increase in the levels of retinol-binding protein (RBP) (Galland, 2010; Anderson, 2010). Therefore, the increase in serum vitamin A is as a result of the transport of the vitamin A from the tissues especially liver where vitamin A is stored to the blood (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). The resultant hypervitaminosis A could manifest in the form of increased activity of osteoclasts causing reduced bone density, liver abnormalities, birth defects in chronic toxicity whereas in acute toxicity it could manifest as blurred vision, nausea, vomiting, vertigo, increase of pressure inside skull, mimicking brain tumour, headaches and muscle incoordination (Galland, 2010; Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). This phenomenon of elevated vitamin A can be teratogenic in women who become pregnant soon after stopping the pills (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Nutritionally, it is important for women on oral contraceptives to be careful on the rich sources of vitamin A especially those from animal origin. Liver is an organ in animals where vitamin A is stored. Studies have

shown that Arctic explorers who have eaten large quantities of polar bear liver became ill and manifested symptoms attributed to hypervitaminosis A (Rolfes *et al*., 2011). The liver is a good source of essential nutrients and eating it occasionally may improve a person's nutrition status (Rolfes *et al*., 2011). But it is important for women on oral contraceptives and pregnant women to take precaution in the intake of liver to avoid nutritional hypervitaminosis A. However, vitamin A plays an important role in human health. Vitamin A is essential for vision, healthy epithelial tissues and growth as well as serves as an important antioxidant which is an important role of beta-carotene. Therefore, to ensure adequate intake of vitamin A, maintaining the recommended dietary allowance (RDA) is important (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Women are generally encouraged to consume healthy diets even as they are on birth control pills (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Other good food sources of vitamin A are green leafy vegetables (spinach, 'kontomire', 'ayoyo', turnip tops, chard and beet greens), green stem vegetables (asparagus, broccoli), yellow vegetables (carrots, sweet potatoes and winter squash) and yellow fruits (apricots, peaches and cantaloupe, mango) and palm oil (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Effects of oral contraceptives on vitamin B2 (Riboflavin) status: Studies conducted in women, showed that oral contraceptive pill users have low vitamin B_2 in plasma and red cells (Presser, 2009). This leads to alteration in the proton transport with the flavin proteins that undoubtedly results to complications in the body (Briggs, 1975; Newman *et al*., 1978; Presser, 2009; Palmery *et al*., 2013). Women who are deficient in riboflavin even before the commencement of oral contraceptives will be predisposed to increased riboflavin deficiency as riboflavin is excreted in the urine daily (Palmery *et al*., 2013). In another study where riboflavin supplements were administered, a significant improvement in pre-existing deficiencies of vitamin B2 in women using low-dosage oral contraceptives was observed (Bamji *et al*., 1985). Therefore, the results of these studies suggest that riboflavin supplementation is advised in women using oral contraceptives especially where vitamin intake is inadequate to meet needs and also in areas where glucose-6-phosphate dehydrogenase deficiency is common (Thorp, 1980; Palmery *et al*., 2013).

Riboflavin is a very important ingredient of the flavin nucleotides (flavin mononucleotide FMN) and (flavin-adenine dinucleotide FAD) in the body (Winters, 1992; WHO/FAO, 2004; Presser, 2009). These components act as coenzymes in proton transport with flavin proteins. The FAD is the number one coenzyme in the flavin protein glutathione reductase, which catalyzes the reduction of oxidized glutathione (Belko *et al*., 1983, 1984, 1985; Winters *et al*., 1992; Soares *et al*., 1993; Presser, 2009; WHO/FAO, 2004). Also vitamin B2 is essential for cell respiration, red blood cell formation, antibody production and the metabolism of carbohydrates, fats and protein. It is good for eye health, tissue repair and healthy skin (Winters *et al*., 1992; Presser, 2009; Galland, 2010).

Deficiencies are caused by low intake among lower-income women of child-bearing age who may not have access to good food sources, such as milk, meat and dark green leafy vegetables and those deficient in nutritional knowledge (Presser, 2009). Vitamin B2 deficiency may also result to lesions around the mouth and tongue, eye and vision problems, digestive disturbances and impaired red blood cell formation resulting in anemia (WHO/FAO, 2004; Mahan and Escott-Stump, 2008; Presser, 2009; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Nutritional management strategies recommend that women who take oral contraceptives should plan to consume foods that are rich in riboflavin. Good sources include milk and milk products (yogurt, cheese); whole-grain, fortified, or enriched grain and cereal products, yeast, dark green leafy vegetables (such as broccoli, turnip greens, asparagus and spinach) and liver (caution must be taken in the intake of liver due to the risk of vitamin A toxicity) (Mahan and Escott-Stump, 2008; Anderson, 2010; Mahan *et al*., 2012; Rolfes *et al*., 2011). Adequate vitamin B2 intake is best achieved through an adequate diet. However, in settings where adequate intake cannot be achieved, supplements may be needed. RDA is mostly between 1.1 to 1.6 mg/day for females 19 years or above and whether or not she is pregnant or lactating (WHO/FAO, 2004).

Effects of oral contraceptives on vitamin B6 (Pyridoxine, pyridoxal, pyridoxamine) status: Oral contraceptives also have an interaction on tryptophan and vitamin B6 function. The intake of oral contraceptives like estrogens and glucocorticoids prior to pregnancy alters tryptophan metabolism as a result of induction of the rate-limiting enzyme, tryptophan 2, 3-dihydroxygenase in the liver (WHO, 1974; WHO/FAO, 2004; BNF, 2009). This phenomenon results in diverting course of tryptophan down its major catabolic pathway, thus nicotinic acid ribo-nucleotide pathway. The observation is that estrogens and pregnancy exert this effect by elevating glucocorticoid activity in the liver. As a result, the elevated metabolism of tryptophan via the niacin pathway, then leads to increase urinary metabolites of tryptophan due to the oral load of tryptophan (WHO, 1975; WHO/FAO, 2004; BNF, 2009).

Findings have shown that, there is an alteration in the metabolism of vitamin B6 in women who take oral contraceptives. These findings are based on the analyses as well as on measurements of how much vitamin B6 is lost from the body through urine (Anderson, 2010).

Biochemical reaction involving the bio-transformation of tryptophan into its excretory products require pyridoxal phosphate (PLP) as coenzyme. The PLP is the coenzyme form of vitamin B6 and this contains a considerable percentage of vitamin B6 compounds present in human blood. Therefore, requirements of this co-enzymes are increased as a result of altered metabolism of tryptophan. Further increased requirement arises because of the fact that, estrogens conjugates compete for PLP binding sites on the Apo-enzyme (WHO, 1975; WHO/FAO, 2004; BNF, 2009). Vitamin B6 therefore, forms part of coenzymes PLP (pyridoxal phosphate) and PMP (pyridoxamine phosphate) required for fatty acid and amino acid metabolism, helps to convert tryptophan to niacin and to serotonin. Also it is important for production of antibody, DNA and RNA activity, conversion of glycogen to glucose and formation of red blood cell. However, it is more essential in the significant role it plays in the production of protein, hormone and neurotransmitter (Mahan and Escott-Stump, 2008; Presser, 2009; Rolfes *et al*., 2011; Mahan, *et al*., 2012). Deficiency symptoms of vitamin B6 include: scaly dermatitis, anaemia, depression, confusion and convulsions (Mahan and Escott-Stump, 2008; Presser, 2009; Rolfes *et al*., 2011; Mahan *et al*., 2012). All these may not occur in one individual at the same time.

Nutritionally, the current recommendation is that, the deficiencies observed consequent to the use of birth pills does not actually permit increased intakes of vitamin B-6 above the RDA for women in various age groups. Women who take oral contraceptives have a different form of vitamin B-6 in the blood similar during pregnancy (Anderson, 2010). Recommended nutrient intake (RNI) for non-pregnant adult, pregnant and lactating women are 1.3, 1.9 and 2.0 mg/day, respectively (WHO/FAO, 2004). Women are encouraged to consume adequate sources of vitamin B6 in a day to improve and help maintain normal levels. Vitamin B6 rich foods are Meats, fish, poultry, potatoes and other starchy vegetables, legumes, non-citrus fruits, fortified cereals, liver, soy products (Rolfes *et al*., 2011). It is shown that 80% of women taking oral contraceptives have abnormal tryptophan metabolism attributable to the relative vitamin B6 deficiency. This can be corrected by given 20-30 mg of vitamin B6 daily which represents 10-15 times normal dietary intake of vitamin B6 (Galland, 2010).

Effects of oral contraceptives on folate status: Folate is another very important micronutrient that women using oral contraceptives risk losing, leading to folate deficiency. Folates play an essential role in the production of DNA in the body. The DNA is responsible for cell division and making new cells in the body. Deficiency of folic acid leads to abnormal cells to be produced especially where a high rate of turnover occurs, like the bone marrow. Thus, a deficiency of folic acid leads to low production of red blood cells, smooth red tongue, mental confusion, weakness, fatigue, irritability, headache, shortness of breath, elevated homocysteine (a risk factor for cardiovascular diseases) and lethargy (WHO/FAO, 2004; Presser, 2009; Rolfes *et al*., 2011). There has been a number of studies that recorded an increased incidence of megalobastic anaemia in women using oral contraceptives, but is still not clear their folate levels before uptake of contraceptives (Presser, 2009; Galland, 2010). The findings from the WHO (Galland, 2010) report concluded that the serum of women using contraceptives contain proteins that binds folate, this folate binder is seen as probably induced by the contraceptive and hence folate deficiency. In several cases, women taking oral contraceptives developed folic acid deficiency (Anderson, 2010). Also it is observed that, this deficiency occurs more in women who had low intake of folic acid or has challenges with intestinal absorption prior to uptake of oral contraceptives (Anderson, 2010). Some oral contraceptives contain folic acid (Anderson, 2010). Women who become pregnant within six months of discontinuing oral contraceptives, are more prone to folate deficiency during the pregnancy than non-users (Shojania, 1971).

Nutritional management of folates deficiency in women on these pills is done by regularly consuming good sources of folates (Anderson, 2010). Folic acid supplementation is extremely important for women preparing to become pregnant or those who become pregnant shortly after they stop taking oral contraceptives to prevent neural tube defects which occurs within the first 28 days of gestation (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Recommended nutrient intake (RNI) for folate are 400, 600 and 500 micrograms/day for non-pregnant, pregnant and lactating women (Sedgh *et al*., 2007). Thus for those women who are pregnant, meeting this recommendation daily from the diet is difficult so as part of pregnant health care services, folate supplement may be given to augment intakes to meet desired outcomes. Women are encouraged to increase the consumption of good food sources of folates such as fortified grains, leafy green vegetables, legumes, seeds and liver to prevent deficiencies especially when they are on birth pills (Anderson, 2010; Rolfes *et al*., 2011).

Effects of oral contraceptives on vitamin B12 (cobalamin) status: Research findings have indicated low serum vitamin B12 levels in women using oral contraceptives, but however red cells were normal (Galland, 2010). Vitamin B12 functions as part of

coenzymes methylcobalamin and deoxyadenosylcobalamin used in new cell synthesis, aids to maintain nerve cells, reforms folate coenzyme, helps to break down some fatty acids and amino acids (Rolfes *et al*., 2011). It is very instrumental in nerve tissue metabolism and in the healthy formation of red blood cells and oxygen transport (BNF, 2009; Presser, 2009). Therefore, women using oral contraceptives for a long time may experience symptoms like anemia, irritability, nervousness, fatigue, brain dysfunction and memory problems, depression and mood changes (Rolfes *et al*., 2011).

The nutritional management is to ensure adequate vitamin B12 intakes for women on oral contraceptive pills. It is recommended that they should consume good sources of this nutrient per the RDA levels. The recommended nutrient intake (RNI) of vitamin B12 is placed at 2.4 microgram/day for adult non-pregnant women, 2.6 for pregnant and 2.8 for lactating mother (Newman *et al*., 1978; Food and Nutrition Board, Institute of Medicine, National academy of Sciences, 1998). Rich food sources of Vitamin B12 are Foods of animal origin (meat, fish, poultry, shellfish, milk, cheese, eggs) and fortified cereals (Rolfes *et al*., 2011).

Effects of oral contraceptives on vitamin C (ascorbic acid) status: A number of biochemical studies indicated that, oral contraceptives intake results to lower mean plasma, white cells and platelet vitamin C levels (Galland, 2010; Anderson, 2010). Mean reduction is approximately 30-40% in those studies (Galland, 2010; Anderson, 2010). In another study, Authors reported that, with adequate dietary intake of vitamin C, women on oral contraceptives would be able to meet their need and hence can maintain a normal ascorbic acid status for periods of six months to seven years (Hudiburgh and Milner, 1979). This situation however, may not be the same for women whose dietary intake is not enough to meet their needs. Also those with unhealthy habits or a pathology of malabsorption may also experience deficiency (Veninga, 1984).

A study by Zal and his colleagues reported that there is significant increase in plasma malondialdehyde levels, related with decreased activities of glutathione peroxidase (GPx) and glutathione reductase (GR) in women on low-dose oral contraceptives when compared to the control group, this however, is suggestive that there is increased oxidative stress induced by the hormonal therapy. It was further reported in the study that supplementation with vitamins C and E significantly increased GPx and GR activity and reduced plasma malondialdehyde levels in women on low-dose oral contraceptives, therefore, signifying that supplementation with these vitamins may be cardiovascular risks protective induced by contraceptive drugs (Zal *et al*., 2012).

Researchers determined the amount of ascorbate in plasma leukocytes, platelets and whole blood entities to evaluate the effect of oral contraceptives on ascorbic acid status. Research findings have shown that vitamin C levels in platelets and leukocytes are lowered by the use of oral contraceptives, specifically those containing estrogens, which is suspected to increase the rate of metabolism of vitamin C (Webb, 1980; Matsui and Rozovski, 1982; Veninga, 1984; Galland, 2010). It has been proposed that the alteration in the blood levels is the result of an alteration in tissue uptake patterns that result in alterations in the distribution of the vitamin (Thorp, 1980).

Vitamin C in the body is essential for Collagen synthesis (strengthens blood vessel walls, forms scar tissue, provides matrix for bone growth), antioxidant, thyroxin synthesis, amino acid metabolism, strengthens resistance to infection and helps in absorption of iron. Deficiencies in Vitamin C leads to difficulty in wound healing, atherosclerotic plaques, easy bruising, pinpoint hemorrhages, inflamed or bleeding gums, bone fragility, joint pain or swelling, muscle degeneration and pain, excessive hair loss, loose teeth, compromised immunity (frequent infections), anemia, hysteria, depression; rough skin, blotchy bruises (Mahan and Escott-Stump, 2008; Presser, 2009; Rolfes *et al*., 2011; Mahan *et al*., 2012).

The main nutritional management goal is to prevent and correct deficiencies in vitamin C. However, no increase has been suggested per the RDA for vitamin C intake for women who take oral contraceptives beyond what is currently recommended for their age group (Anderson, 2010). Women should increase their intake of fruits rich in vitamin C or 500 mg of vitamin C daily if oral intake is inadequate to normalize the blood and tissue levels (Anderson, 2010; Mahan and Escott-Stump, 2008; Mahan *et al*., 2012). Dietary sources of rich vitamin C are citrus fruits and juices, strawberries, cantaloupe, pineapple, broccoli, peppers, brussels sprouts, spinach, cabbage and guava (Anderson, 2010; Mahan and Escott-Stump, 2008; Mahan *et al*., 2012).

Effects of oral contraceptives on vitamin E (tocopherols) status: In a preclinical study, the administration of contraceptive steroids significantly reduced plasma tocopherol levels and increased dietary requirements for vitamin E in rats (Aftergood and Alfin-Slater, 1974). A study by Akinsanya and colleagues (Akinsanya *et al*., 2010) revealed that vitamin E and folic acid significantly decreased in antioxidant markers induced by the combined oral contraceptives in rats (Akinsanya *et al*., 2010). Also in another study, a combined-type oral contraceptives reduced plasma tocopherols in healthy Caucasian women and, hence, recommended that women on oral contraceptives should

be given vitamin E supplements (Briggs, 1975). Renaud and friends (Renaud *et al*., 1987) in their studies concluded that the platelet hyperactivity of long term oral contraceptive users might be dependent on a low level of platelet alpha-tocopherol which administering a vitamin E supplement can overcome this effect.

Vitamin E is a fat-soluble vitamin and an antioxidant (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Vitamin E functions as one of the body's primary defenders against the adverse effects of free radicals (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). The major role is to terminate the chain reaction of free radicals producing more free radicals (Rolfes *et al*., 2011). Hence, vitamin E protects the vulnerable components of the cells and their membranes from destruction by free radicals (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Vitamin E have been noted to prevent the oxidation of the polyunsaturated fatty acids, also it protects other lipids and related compounds as well (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Research findings suggests that vitamin E may reduce the risk of heart diseases by protecting low-density lipoproteins (LDL) cholesterol against oxidation and decreasing inflammation (Rolfes *et al*., 2011). Low-density lipoproteins oxidation and inflammation have been implicated as key factors in the development of cardiovascular disease (Mahan and Escott-Stump, 2008; Rolfes et al., 2011; Mahan *et al*., 2012). Deficiency of vitamin E could manifest in red blood cell breakage and nerve damage (Rolfes *et al*., 2011).

The main nutritional management strategy is to prevent and correct deficiencies in vitamin E. Hence, vitamin E supplements have been recommended for women on oral contraceptives, (Briggs, 1975; Renaud *et al*., 1987) however, they are expected to maintain the RDA (15 mg/day) (Rolfes *et al*., 2011) to avoid toxicity as this vitamin can be stored in the body because it is a fat soluble vitamin (Mahan and Escott-Stump, 2008). Good food sources of vitamin E include: polyunsaturated plant oils (margarine, salad dressings, shortenings), green leafy vegetables, wheat germ, whole grains, liver, egg yolks, nuts, seeds, fatty meats (Rolfes *et al*., 2011).

Minerals

Effects of oral contraceptives on iron status: Iron is also one major micronutrient which have been observed by several studies to lead to lower amount in women who take birth control pills (Rutstein, 2005; Anderson, 2010). Some women using oral contraceptives lose less amount of blood during menstruation. The importance of iron is that, it is needed to make hemoglobin, for oxygenation of blood (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012). Therefore, it means that, less amount of blood lost during menstruation means less blood needs to be manufactured leading to iron deficiency anaemia (Anderson, 2010).

As far as RDA for iron is concerned, women of childbearing age is 18 mg/day. According to the Institute of Medicine, the recommendation for women taking oral contraceptives is 10.9 mg/day (Institute of Medicine or the National Academies, Subcommittee on Interpretation and Uses of Dietary Reference Intakes and Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2003). However, women on birth pills do not need to reduce consumption of iron-rich foods (Anderson, 2010). They should also consider taking multivitamins that contain iron (Institute of Medicine or the National Academies, Subcommittee on Interpretation and Uses of Dietary Reference Intakes and Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2003). Sources of iron in the diet are Meat, poultry, liver, fish, whole grain and enriched cereals and cereal products, dried beans and peas, prune juice, deep green leafy vegetables (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Effects of oral contraceptives on zinc status: Studies conducted over several decades since 1968 have shown that plasma zinc levels are reduced in women on oral contraceptives than women who were not (Halsted, *et al*., 1968; Briggs *et al*., 1971; Prasad *et al*., 1975; Prema *et al*., 1980; King, 1987; Fallah *et al*., 2009; Akinloye *et al*., 2011). However, the levels in red blood cells are reportedly increased in oral contraceptive users (Anderson, 2010). It is assumed that the decrease in serum zinc could result in a decrease of tissue zinc levels owing to alterations in zinc absorption, excretion or tissue turnover. If these alterations occur, the dietary zinc requirement would be higher in women using oral contraceptives (Fallah *et al*., 2009).

Zinc supports the functions of many proteins in the body, such as the metalloenzymes, which are involved in a range of metabolic processes, including gene expression regulation (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Also, zinc stabilizes cell membranes, helping to support their defence against free-radical attacks. Zinc also contributes in immune function and in growth and development (Rolfes *et al*., 2011). Zinc does not seem to play a direct role in insulin's action but it actively participates in the synthesis, storage and release of the hormone insulin in the pancreas. Zinc also interacts with platelets in blood clotting, affects thyroid hormone function and influences behaviour and learning performance (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). It is required to synthesize the active form of vitamin A (retinal) in visual pigments

and the retinol-binding protein for vitamin A transport (Rolfes *et al*., 2011). It is important for normal taste perception, wound healing, the production of sperm and foetal development. A zinc deficiency mars all these and other functions, underlining the vast importance of zinc in supporting the body's proteins (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Symptoms of deficiency include: growth retardation, delayed sexual maturation, impaired immune function, hair loss, eye and skin lesions and loss of appetite (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

The RDA for zinc for women users of oral contraceptives is the same as that of those not using pills. RDA of zinc for adult women of average weight are 3.0, 4.9 and 9.8 mg/day depending on whether or not zinc source is of high bioavailability, moderate bioavailability and low bioavailability respectively (WHO/FAO, 2004). Good sources of diet rich in zinc are Oysters and other seafood, meat, nuts, whole grain breads (Mahan and Escott-Stump, 2008; Anderson, 2010; Mahan *et al*., 2012).

Effects of oral contraceptives on copper status: The copper levels in the plasma increases considerably in women using birth control pills (Anderson, 2010; Watts, 1989). It has been reported that ceruloplasmin-a copper-carrying protein destroy vitamin C by oxidation (Anderson, 2010). This increased blood copper levels as a result of uptake of contraceptives may lead to reduced levels of blood vitamin C levels (Anderson, 2010). If there is deficiency in vitamin C, the effects have been discussed above in the section of vitamin C. Copper is a trace mineral that helps form haemoglobin and part of several enzymes: *Ceruloplasmin a* copper-containing enzyme participates in the oxidation of ferrous iron to ferric iron, two copper-containing *superoxide dismutase* enzymes defend against free radicals, l*ysyl oxidase another* copper-containing enzyme helps synthesize connective tissues and *cytochrome C oxidase a* copper-containing enzyme participates in the electron transport chain (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Animal studies have shown that copper deficiency raises blood cholesterol and damages blood vessels, hence proposing that low dietary copper might contribute to cardiovascular disease in humans (Rolfes *et al*., 2011). However, further studies are need to confirm this. Copper toxicity is unlikely through excessive dietary intakes, however, toxicity may result from excessive intakes from supplements (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Toxicity do not only result in vitamin C deficiency (Anderson, 2010) but it is established that it may cause liver damage (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Good dietary source of copper are oysters and other seafood, liver, nuts, dried beans, peas and dried fruits (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012; Rolfes *et al*., 2011). Supplements are not recommended for women on oral contraceptives. The dietary sources are to be consumed in moderation not exceeding RDA (900 µg/day) (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012) or even lower when there is toxicity.

Effects of oral contraceptives on sodium status: The production of angiotensinogen is stimulated by estrogens resulting to increased levels of angiotensin and aldosterone and thus sodium retention (Oelkers, 2002; Smals, 2000; Palmery *et al*., 2013). Progesterone is a potent aldosterone antagonist, which acts on the mineralocorticoid receptor to prevent sodium retention. In combined oral contraceptives, progestogens devoid of antimineralocorticoid and antiandrogenic activity are unable to counteract the sodium-retaining effect of the ethinylestradiol component. As a result, these preparations may increase fluid retention and promote related symptoms such as oedema and increased body weight (Oelkers, 2002; Smals, 2000; Vaiarelli and Carlomagno, 2013). Oral contraceptives therefore, increases the sodium level predisposing users to hypertension and cardiovascular disease risk (Palmery, *et al*., 2013).

Sodium is a major mineral and it is the primary cation of the extracellular fluid and the principal regulator of its volume (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Sodium also aids maintain acid-base balance and is crucial to nerve impulse transmission and muscle contraction. Sodium is readily absorbed by the intestinal tract and moves freely in the blood until it reaches the kidneys, which filter all the sodium out of the blood. Then, the kidneys return to the bloodstream the exact amount of sodium the body needs with great precision. The amount excreted is normally equivalent to the amount ingested on a given day. When blood sodium rises such as when a person eats salted foods, thirst signals the person to drink until the appropriate sodium-to-water ratio is restored. Then the kidneys excrete both the excess water and the excess sodium together (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Due to the correlation between high sodium intakes with high blood pressure, the Upper Level for adults is set at 2300 milligrams per day (Rolfes *et al*., 2011). Women on oral contraceptives therefore are expected not to exceed this amount of sodium daily. It is important to note that sodium do not just enter our foods from table salt only, but many of our foods, condiments and spices contain sodium. These include: table salt, soy sauce; moderate amounts in meats, milks, breads and vegetables; large amounts in processed foods especially canned foods that are preserved with salt (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Also, sea

fishes like stock fish is also a good source of sodium. Women on oral contraceptives are advised to adopt DASH (Dietary Approaches to Stop Hypertension) diet plan especially if they are already diagnosed hypertensive. However, adopting DASH diet plan will prevent and/or delay the onset of hypertension (Mahan and Escott-Stump, 2008; Rolfes i., 2011; Mahan *et al*., 2012). However, due to the indispensable role of sodium in the body, they are not to avoid foods containing sodium and these foods are also containing other nutrients which are as well important for their health. The symptoms of sodium deficiency are muscle cramps, mental apathy and loss of appetite while toxicity results in oedema and acute hypertension (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012).

Effects of oral contraceptives on selenium status: Result of several studies have revealed that oral contraceptives interfere with selenium absorption and hence, caused lower serum selenium concentrations when compared with control groups (Heese *et al*., 1988; Fallah *et al*., 2009; Palmery *et al*., 2013). Selenium has been suggested to have a beneficial role in the prevention of cancer, especially breast cancer, hence, these findings are very essential (Cann *et al*., 2000; Rejali *et al*., 2007). Selenium is one of the body's antioxidant nutrients, it functions primarily as a part of proteins, particularly, the enzyme glutathione peroxidase (Rolfes *et al*., 2011) and certain forms of thioredoxin reductase found in animals and some plants (Palmery *et al*., 2013). Studies have shown that Glutathione peroxidase and vitamin E functions in tandem (Rolfes *et al*., 2011). Glutathione peroxidase prevents free-radical formation, thus blocking the chain reaction before it begins; if free radicals do form and a chain reaction starts, vitamin E stops it (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012). Also, selenium contributes to the functioning of the thyroid gland and in all the 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 (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012; Palmery *et al*., 2013). Since selenium is an important antioxidant nutrient, deficiency can increase the risk of cancer and cardiovascular disease (Russo *et al*., 1997; Knekt *et al*., 1998) especially predisposition to heart disease characterized by cardiac tissue becoming fibrous (Keshan disease) (Rolfes *et al*., 2011)

Women on oral contraceptives can help prevent selenium deficiency if they pay a particular attention to the consumption of selenium rich foods which include: seafood, meat, whole grains, fruits and vegetables (depending on soil content) (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012; Rolfes *et al*., 2011).

Effects of oral contraceptives on magnesium status: Several studies have repeatedly reported that serum magnesium levels are reduced by oral contraceptives (Olatunbosun *et al*., 1974; Stanton and Lowenstein, 1987; Blum *et al*., 1991; Hameed *et al*., 2001; Akinloye *et al*., 2011). Seelig reported that prophylactic treatment of postmenopausal osteoporosis with estrogens and calcium reduced serum magnesium levels (Seelig, 1990).

Magnesium is classified as one of the major minerals in the body (Rolfes *et al*., 2011). It plays a crucial role in the maintenance of bone health, functions in all the cells of the soft tissues, where it forms part of the protein making machinery and is necessary for energy metabolism and it acts as a catalyst in the body's use of glucose, the synthesis of protein, fat and nucleic acids and the cell membrane transport systems (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Magnesium contributes in hundreds of enzyme systems (Mahan and Escott-Stump, 2008; Mahan *et al*., 2012). Calcium and magnesium work in synergy to bring about muscle contraction and blood clotting: calcium promotes the processes, whereas magnesium inhibits them. This dynamic interaction between the two minerals helps regulate blood pressure and lung function (Mahan and Escott-Stump, 2008; Rolfes *et al*., 2011; Mahan *et al*., 2012). Research have shown that calcium/magnesium ratio is altered when there is depletion of magnesium and this has the potential to affect blood coagulability (Cowan, 1995). Also, it has been postulated that the reduction in serum magnesium levels is one reasons for higher risk of thrombosis while using oral contraceptives (Olatunbosun *et al*., 1974). Magnesium like many other nutrients, supports the normal functioning of the immune system. Other deficiency symptoms include: weakness, confusion and in extreme deficiency may lead to convulsions, bizarre muscle movements (especially of eye and face muscles), hallucinations and difficulty in swallowing (Rolfes *et al*., 2011).

The nutritional management of magnesium deficiency for women on oral contraceptives entail the use of magnesium supplementation during oral contraception (Palmery *et al*., 2013). Also, consumption of good food sources of magnesium such as nuts, legumes, whole grains, dark green vegetables, seafood, chocolate and cocoa is very crucial however, the RDA for women (310 mg/day) (Rolfes *et al*., 2011) should be maintained except when there is markedly deficiency but upper tolerable limit (350 mg non-food magnesium/day) (Rolfes *et al*., 2011) should not be exceeded.

Conclusions: Studies spanning for more than four decades (early 1970s) have demonstrated that the use of oral contraceptives results in depletion of micronutrients which probably contributed to many common adverse side effects experienced by the users. Hence, this review has

shown that the first line of action for micronutrient deficiency induced by oral contraceptives on users by clinicians is to prescribe intake of appropriate dietary supplements (Palmery *et al*., 2013). This is necessary because of the variation in bioavailability of the nutrients from food sources and the impairment of the absorption induced by oral contraceptives. An appropriate dietary supplement should contain vitamins of the B complex together with folic acid, vitamin E and C as well as minerals such as magnesium, iron, zinc and selenium. However, an adequate diet is recommended for people on oral contraceptives because this will help them to meet their nutritional needs. A professional assistance from a registered dietitian/nutritionist will help them plan a healthy meal. Further research is needed to compare the effects of food sources of these affected micronutrients and the dietary supplements for women on oral contraceptives.

Competing interests: Authors declare that there is no competing interest.

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