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The Effects of Oral Contraceptives on Nutrient Status, with especial Consideration to Folate

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ABSTRACT

Oral contraceptives (OCs) are widely used by a significant number of women, often commencing at early adolescence. Whilst most research has investigated the physiological effects of OCs, some studies have identified impacts upon nutritional status of certain vitamins and minerals. In this context, a report published by the World Health Organization (WHO) is relevant, since women who take OCs-especially in less well-developed countries might not always have adequate diet. Furthermore, women whose life style is unhealthy, those with mal-absorption pathologies, or have genetic polymorphisms that affect vitamin metabolism might also be at risk of the negative impacts on an individual's nutrient status. This literature review investigates the effects that oral contraceptives might have upon nutrient status. It identifies potential interactions with Vitamins A, B1, B2, B6, B12, C and E and folic acid as well as magnesium, zinc, selenium, copper, co-enzyme Q10 and beta-carotene status. It then examines the possible consequences that induced depletion of folic acid might cause with especial focus on neural tubes defects in UK, where food supplementation with this vitamin is not yet mandatory. It suggests that in those using this form of contraception or hormone replacement therapy, it is valid to consider appropriate nutritional supplements as a complementary first line strategy in order to prevent possible vitamin and mineral deficiencies.

Keywords: Oral contraceptive pill, Vitamins, Micronutrients, Minerals, Folate

INTRODUCTION

Oral contraceptives (OCs) are nowadays some of the most frequently consumed drugs in many countries in the developed world and are considered some of the most effective medications currently available [1]. Combination formulations containing both oestrogens and progestins are the most frequently used. The most commonly used oestrogens are Ethinyl estradiol (EE) and mestranol, with the former the more popular. The combination of hormones is designed to prevent ovulation [2]. Since their introduction, manufacturers have sought to minimize side effects in order to improve compliance without impairing efficacy [3,4]. In the low-dose formulations currently used today, combinations of a progestin and EE at a dose of ≤ 35 mcg are commonplace, with doses as low as 20 mcg capable of to delivering efficacy without the side-effects of bloating and breast tenderness, usually associated with oestrogenic activity [5,6].

Over the past 5 decades interest has grown in possible modifications in nutrient status and/or metabolic processes that might be induced as a result of the extensive use of OCs and a publication by the World Health Organisation highlights that these effects are of high clinical relevance [7-11]. However, the component responsible for these changes remains yet to be identified [12,13].

METHODS

A search was conducted of electronic databases of literature published through March 1, 2019. Initially, the search strategy consisted of out using keywords and Medical Subject Headings (MeSH) "oral contraceptives" and "nutrient interactions" and "vitamin interactions". Using references from this primary search, additional terms included "vitamin A", "vitamin B1", "vitamin B2", "vitamin B6", "Vitamin C", "Vitamin E", "folic acid", "vitamin B12, "copper", "magnesium", "selenium", "zinc", "co-enzyme Q10", "beta-carotene" were subsequently added and searched. Other references or review articles identified

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within the primary research were also examined.

RESULTS

Vitamin A

It is suggested that estrogens elevate retinol binding protein production, which transports vitamin A in the blood and this may result in vitamin A being removed from storage sites such as the liver [14-17].

Vitamin B1

Reports have identified that in women taking oral contraceptives, activity of the thiamine-dependent enzyme-erythrocyte-transketolase is somewhat reduced, possibly resulting in possible thiamine deficiency, whilst others do not concur [17-20]. One study in women using 500 mcg dl-norgestrel and 50 mcg EE examined the additional needs of thiamine, pyridoxine and riboflavin required to stabilise their status [21]. It found that daily supplementation with 2 mg riboflavin and 3 mg thiamine mitigated any declines in nutritional status, whilst pyridoxine at a daily dose of 10 mg was able to correct defects in tryptophan metabolism.

Vitamin B2

It is thought OCs may impact upon the absorption of riboflavin or interfere with metabolism to the active coenzyme species [22,23]. In addition, reduced urinary excretion of vitamin B2 or lowered activity of erythrocyte glutathione reductase-indicative of riboflavin deficiency-was observed in those using OCs [16,18]. Vitamin B2 deficiency is commonly associated with low socioeconomic status and it has been shown that in groups of these women of child bearing age that this state is aggravated by the use of OCs [16,22]. Deficiencies of riboflavin in women using low-dose formulations have been shown to be corrected by supplementation of the vitamin [24]. However, others have reported, no interaction with OCs when dietary riboflavin intake is adequate [19,20,25]. These observations suggest that in situations where women are taking OCs and nutrition is limited supplementation should be considered [17]. Given that headache is a commonly experienced side effect of OC's, reports that riboflavin supplementation decreases headache intensity, frequency and duration, as well as intake of medication, suggest that such a strategy might also prove of benefit [26].

Vitamin B6

Both OCs and estrogen replacement therapy have been reported to negatively impact upon metabolism of pyridoxine and reduce levels of the activated co-enzyme forms of the vitamin-pyridoxamine 5' phosphate (PMP) and Pyridoxal 5' phosphate (PLP) [15,27-35] however others have found otherwise [36,37]. Evidence that OC's reduce plasma PLP levels comes from a large observational study which identified this relationship in 75% of women who did not take supplements [34] and led to speculation that this situation might be the cause of the heightened risk of venous thromboembolisms observed in those taking OCs [32]. More recently, reports suggest that even those using more modern lower-dose OCs may require supplementation to optimise their vitamin B6 status [13]. However, this is debated by other investigators argue that levels might return to normal vitamin B6 status despite continued therapy [37]. Some authors also suggest low pyridoxine levels may contribute to side effects such as depression, lethargy and fatigue [15,27,30]. In situations where plasma PLP concentrations are suboptimal and in subsequent pregnancy and lactation, at 5 months gestation, at delivery and later in breast milk ,this situation has been shown to be perpetuated in those who have taken OC for more than 30 months [38].

Folic acid

Shortly after the introduction of OCs, studies appeared in the literature to suggest their consumption might negatively impact on user's folate status [39-43]. For example, in 1968 Shojania et al. [44] reported in Lancet that in comparison to a control group, mean serum folate in OC users was lower and that the numbers of subnormal folate levels was higher too. They also reported that the rate of decrease in mean serum folate levels increased with longer duration of use of OCs, but within 3 months of cessation of use, levels of folate returned to baseline. Likely mechanisms that have been suggested for these observations include the possibility that OCs might cause folate polyglutamates to be malabsorbed and/or increase the rate of urinary excretion of folates, and/or accelerate folate metabolism through an induction of microsomal enzymes that metabolise folic acid [43]. Further studies have confirmed these reports, although others have yielded equivocal findings [45-47]. Potential confounders contributing to these different results might include differences in dietary intake, duration of use and compliance with OCs, use of tobacco and alcohol, and the use of dietary supplements [45]. A recent meta-analysis and systematic review concluded "Because of the reduction in blood folate concentrations associated with the use of oral contraceptives, it is critical for women of childbearing age to continue folate supplementation during oral contraceptive use" [48]. In 2012, in recognition of this, an oral contraceptive fortified with folate was made available in some markets as a means of lowering the hazard of neural tube defects (NTDs) in females who might become pregnant during OC use or shortly after discontinuation [49,50]. Evidence also suggests that OCs might enhance the rate of progression of cervical dysplasia to cervical cancer, and folic acid may be able reverse or reduce the rate of progression of this dysplasia [51,52].

Vitamin B12

A number of studies of women using OCs have identified mean serum vitamin B12 levels lower than in nonusers [13-15,32,43,53-58]. However this has not been replicated in others after up to 6 months of use [28,59,60]. It is has been

reported that in women using OCs, that whilst absorption and the urinary excretion of vitamin B12 were normal, the total binding capacity for the vitamin in the serum is significantly reduced and that the levels of a glycoprotein which protects vitamin B12 from stomach acid degradation-transcobalamin I-was also reduced compared to non-OC users, suggestive of them being the causative factors for these observations [43,56]. In a later study, OC consumption was found to be associated with reduced concentrations of vitamin B12 in serum, with time point discrepancies continuing over 12 weeks [61].

Just as impaired folate status is an independent NTD risk factor, inadequate maternal cobalamin status is similarly problematic [62]. This is possibly due to elevated Methylmalonic acid (MMA) levels, frequently observed in the onset of vitamin B12 deficiency. Indeed, serum MMA levels >90th percentile at mid-trimester have been reported to have a 13-fold increased risk for a pregnancy resulting in a NTD [62]. However, not all authors reports alterations in MMA concentrations in the urine [63] or plasma homocysteine or MMA concentrations in those using OCs compared to non-users [56,64].

However, a systematic review concluded that OCs do indeed exert a negative influence on vitamin B12 status [65] supporting the concept that supplementation might be considered in OC users [66], especially in those with an unhealthy lifestyle or inadequate diet, and although cessation of OC use results in normalisation of levels of the vitamin [59], there are those who suggest clinicians should recommend appropriate dietary supplementation as a primary approach to counter potential deficiencies of key vitamins and minerals in OC users [67].

Vitamin C

It is thought estrogen can increase vitamin C metabolism, and it has been reported that the use of OCs reduces levels of this vitamin in leukocytes and platelets [27,57,68,69] with alterations in tissue uptake patterns and changes in the distribution [17]. In one instance it was shown that over periods of six months to seven years there is no compromise of vitamin C status providing adequate dietary intake of ascorbic acid is maintained [70]. However, this might not always be the case in situations where unhealthy lifestyles, poor diet or mal-absorption pathologies occur [57]. Recently, in women taking low-dose OCs, it was reported that compared to controls the former group experienced significantly elevated levels of malondialdehyde levels in the plasma, which were associated with a reduction in glutathione peroxidase and reductase ezymes and indicative of increased oxidative stress [71]. However, supplementation with vitamins C and E significantly reversed these changes [71]. It is possible that estrogens can both reduce the absorption of vitamin C and/or accelerate its catabolism and that stores might be mobilised in the tissues to prevent oxidation of estrogens [17,72,73].

Vitamin E

The administration of contraceptive steroids in preclinical models, reduced levels of plasma tocopherol levels, significantly and also increased vitamin E dietary requirements [74]. Later studies found that supplementation of this vitamin together with folic acid, significantly lessened the OC induced oxidative stress in women using this form of contraception [75], leading other authors, following similar observed outcomes, to recommend women taking these drugs to supplement with vitamin E [76]. Other researchers have found a significantly higher level of platelet clotting activity in conjunction with a reduction in vitamin E plasma levels in OC users which was reversed with administration of the vitamin [77,78].

Magnesium

Estrogens lower serum levels of magnesium as a result of increasing uptake by bones and soft tissues resulting in an inverse relationship between the two [79-81]. Estrogen therapy, whether through use of OCs or HRT, reduces levels of serum and can result in hypomagnesemia, particularly in those with a low dietary intake of the mineral or as a result of other causes of its loss [79,81-85]. The depletion of magnesium can subsequently alter the ratio of calcium/magnesium ratio which in turn can affect blood coagulation [86] which supports the view that magnesium supplementation might be considered with OCs, since it is possible that hypomagnesemia might be associated with thromboembolic side effects associated with estrogens [78,79].

Zinc

50 years ago, lower levels of zinc were identified in the plasma of OC users in comparison to those not prescribed them [87], an observation to be confirmed in later studies likely due to changes in absorption, tissue turnover or excretion [12,88-91]. Because estrogen can induce a reduction in serum albumin, this may cause a decrease in the concentration of zinc transported in the blood [88,92]. Although this effect is not conclusively reported, the majority of studies support the view that even low dose oral contraceptives negatively affect the nutritional status of this mineral [12,15,68,90,91,93-98]. Moreover, a recent systematic review concluded “a decrease in the serum concentrations of zinc, selenium, phosphorus and magnesium have been reported in OC users with reductions proportional to the duration of contraceptive use”; suggesting supplementation might be warranted [65].

Selenium

One study of OCs contraceptive pill users, observed that in addition to a significant reduction in serum zinc levels, there was a similar negative, but not statistically significant alteration in selenium level [91]. In a cross-sectional randomized study of women using oral contraceptives,

injectable or hormonal intra-uterine devices, mean serum selenium levels of all these subjects were significantly lower than controls [82].

Calcium

Several authors have reported use of OCs by women of young adulthood through to peri-menopause may have a beneficial effect on bone-mineral density (BMD) [99-102] through reducing short and long term calcium excretion [103-105]. However, again this has not been reported by all investigators with some suggesting age at first use [106], physical activity and race [107] might be major factors affecting this relationship. This view is supported in a study of cross-sectional design of women aged 20-35 year which identified that individuals with the highest BMD were short-term OC users that participated in long-term exercise, whereas long term exercisers and OC users did not experience the same benefits [108]. In another, two year, intervention study, OC users were randomized into two groups, one exercising and the other not exercising and compared with similarly allocated nonusers. Here total BMD was elevated in those exercising but lower in users OC's, and OC use in combination with exercise delivered an effect that was less suppressive on mechanical strength at the femoral neck and normal accretion of bone mass [109]. Similar outcomes were observed by Weaver et al. [110]. A subsequent one year investigation examined the effect that various doses of calcium supplementation had on BMD in 18 to 30 year old females using OCs when compared to non-OC users. It reported a calcium intake of 1000-1100 or 1200-1300 mg/d from products of a dairy origin provided OC users greater protection from total spine and hip BMD loss than in those consuming <800 mg/d [111].

Copper

A recent meta-analysis demonstrates even the more recently developed OCs containing, EE doses of 25-30 mcg frequently raise serum copper levels by approximately 50% to the between 1.5 and 2 mg/L [112].

Co-enzyme Q 10, vitamin E and β-carotene

A 2010 study compared the effects of three methods of contraceptive (OC, transdermal patch and vaginal ring) on serum levels of α- and γ-tocopherol, co-enzyme Q 10 and total antioxidant capacity (TAOC) in premenopausal women [113]. In all three types of contraceptive users, serum levels of α-tocopherol and coenzyme Q10 were observed to be significantly reduced compared with controls. Other authors had also previously described the similar effects of HRT in decreasing serum levels of α-tocopherol and coenzyme Q 10 [114]. Estrogen has also been demonstrated to be associated with reduced serum concentrations of certain antioxidants that are lipid soluble [115,116]. The same group also reported that users of OCs had significantly lower levels of plasma β-carotene [116].

DISCUSSION

The above narrative indicates that oral contraceptive may impact upon nutritional status of users and here the possible implications of these effects are examined in a contextual setting.

Hormonal contraceptive use

Combined oral contraceptives (COCs), are among the most common contraceptive methods used worldwide by about 9% of married women or those in a relationship aged 15 to 49 years [117]. They are highly effective if used consistently and correctly, but their failure rate with typical use is much higher [118]. The most recent UK Office for National Statistics (ONS) survey identified OCs accounted for 25% of the total female use [119]. A 2013 UK study investigated adolescents aged 12-18 years and found that around 20% of these females received prescriptions for OCs, most of which were for a combined oral contraceptive (COC) [120]. However, a 2010 study found an increasing number of women-a five-fold increase in 5 years in UK were also using contraceptive hormone implants and of those, more than half were aged 24 or under [121]. A further study found OCs to be the most widely used method in five European countries [122] with an estimated 22 million users with levels of satisfaction of over 90%. However, nearly 40% of pregnancies in the world are unintended and worldwide, incorrect and inconsistent use of COCs appears to be one of the most common causes of unintended pregnancy [123]. For example, a recent Iranian study showed that 28% of COC users took them incorrectly [124] and more than one-quarter (27%) of unintended pregnancies occurred while using a COC [125].

Side effects of oral contraceptives

A meta-analysis of studies from 19 countries identified COC discontinuation rate is very high, reaching 44% in the first year [126]. The main reasons for nearly half (47%) of discontinuations are due to side effects or health concerns.

Two clinical trials have investigated the effects of daily systemic multivitamin complex and vitamin B6 supplementation on COC side effects [66,127]. Subsequently another study assessed the effect of multivitamin use might have on the rate of continuation of use of OCs and their observed side effects within the first few cycles of use in 332 women [128]. Nausea, mood changes, weight gain and breast tenderness were also significantly less common in the multivitamin group in all cycles, and spotting/irregular bleeding and dizziness were significantly less common in most of the second, third and sixth cycle follow-up. It concluded multivitamin supplements could significantly reduce the side effects of COCs in the initial cycles and improve continuation rates.

Self-reported intakes dietary vitamins B6, B12 and folate were used to examine the relationship between depressions

in women who used OCs [129]. OC users were reported to more depress than counterparts not using OCs, with depression statistically significantly associated with distinct vitamin intake quartile levels. When intakes exceeded RDAs for vitamin B12, folate and vitamin B6 by 75%, 13% and 7%, respectively, OC users were found to be less depressed.

Possibly as a result of these issues, adherence in Western countries to use of OCs is limited, with a 50% rate of discontinuation at 6 months [130,131], with side effects most commonly cited as the reason for discontinuation [130,132,133]. Here weight gain is a reported problem and although some studies have shown that OCs do not have an effect on this issue [134,135], including a recent review by Cochrane [136], it is often reported as a side effect [137]. 40% more females who gained weight have reported discontinuation of OCs compared to those who did not gain weight [131]. Furthermore, an inverse relationship between obesity and micronutrient deficiencies is thought to induce alterations in metabolism of leptin and inflammatory responses [67,138-140]. One investigation [141] assessed almost 40,000 premenopausal Korean females and identified an association of OC use with a 12% increased risk of obesity. Those with intakes of vitamins A, B1, B2, B3, C, folate, calcium, potassium and phosphorus less than recommended appeared particularly susceptible to obesity. The authors concluded efforts should be considered to increase micronutrient intake in females taking OCs.

Oxidative stress and oral contraceptive use

A recent study analysed the impact of OCs on pro/antioxidant status in healthy young women [142]. Typical blood markers of oxidative stress, such as oxidised glutathione oxidized (GSSG), malondialdehyde (MDA), gamma-glutamyltranspeptidase (GGT) and Cu, Cu/Zn ratio were determined and in women taking OCs. This study further confirms that OCs use compromises the pro/antioxidant imbalance. A further publication [143], found OC use did influence copper, iron and zinc homeostasis, but that supplementation with zinc beneficially altered copper utilization in OC users and had a positive effect on oxidative stress.

Lipidemic effects of oral contraceptive

OCs have been shown to directly affect metabolism of lipids and carbohydrate [144-146] with impaired glucose tolerance and insulin secretion, accompanied by elevated levels of total cholesterol and serum triglycerides [147-149]. However, given the differences in the formulations used in these studies-both qualitative and quantitative-their findings remain controversial, as does the potential association between the use of OCs and cardiovascular disease risks [150,151]. It is recognized that both vitamins C and E confer enhanced effects on the profiles of lipids and the impact of the use of COCs on serum lipids in women over 4 weeks has been investigated in one study [152]. Statistically significantly higher increases in the levels of LDL cholesterol and triglycerides and LDL were reported in COC users than non-users. In the group using COCs and receiving vitamins C and E, the HDL/LDL ratio increased as did the HDL level, whilst triglycerides and LDL decreased significantly in comparison to those women in other group.

The nutritional landscape in UK

Given the above data relating to the impact of OCs on the nutrient status of users it is relevant to examine the prevailing nutritional environment within which are they likely to reside. Specifically, a recent UK study identified that 5% of females aged 19-64 had an intake of vitamin A below the lower reference intake, likewise 12% with riboflavin, 23% iron, 8% calcium, 11% magnesium 23% potassium, 4% zinc, 51% selenium, 10% iodine and 21% had a low vitamin D status [153]. 16% of females in the same age group were considered to have folate concentrations below World Health Organisation threshold indicative of folate deficiency, and the proportion of women of childbearing age with red blood cell concentrations of folate below the threshold for elevated risk of neural tube defects (748 nmol/L) was 91% [154].

Folate metabolism and genotype

The enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) is critical in folate metabolism. It converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary form of folate in the circulation and operates as a methyl donor in homocysteine Hcy) conversion to methionine [155]. A C677T polymorphism in the MTHFR gene limits the activity of this enzyme and can cause enhanced thermolability, especially in states of folate deficiency [156]. Mutation homozygous individuals have significantly lower plasma folate levels and elevated plasma Hcy [41,157,158]. It is not surprising that the MTHFR 677T mutation is associated with a higher risk of NTDs [159]. As a result of the recognised relationship between NTDs and suboptimal folate status, many nations have adopted mandatory fortification of the vitamin in products, usually of a cereal grain origin [160]. This has resulted in increased levels of serum folate and consequently lower Hcy concentrations [161,162] and reduced rates of NTDs [163,164] at the population level, but there are still some subgroups, particularly fertile young females, with an ongoing suboptimal intake of folate despite this fortification and ready access to vitamin supplements [165,166]. Uncertainty remains regarding optimal folate intake for those carrying MTHFR 677TT polymorphism, which probably require an increased levels, especially where folate status is already low [167]. Studies of men of Mexican-American origin suggested that 400 mcg of dietary folate equivalents per day (where, 1mcg DFE=1 mcg food folate or 600 mcg folic acid with food) was inadequate for TT subjects [168,169]. Therefore, in pregnancy recommended intakes vary from country to country from 355 to 800 μg/day

dietary folate equivalents [170], with a number of authorities taking genetic susceptibility to suboptimal status of folate into consideration. Hence, in Australia, the recommended dietary intake for pregnancy is 600 µg/day DFEs [171]; whilst for women with an increased risk of NTDs at birth and folate deficiency, the South Australian Perinatal Practice Guidelines make a recommendation of a daily total folate intake of 5mgs. Here, high risk is deemed to include those with an identified MTHFR polymorphism [172]. This is supported by a 2017 meta-analysis that confirms a MTHFR TT genotype to be associated with lowered serum folate levels, increased plasma homocysteine as well as a reduced response to supplementation at daily doses from 400 mcg over short term time periods [173].

Folic acid, neural tube defects and small-for-gestational age neonates

The benefit of folic acid supplementation in preventing NTDs, including anencephaly, encephalocoele and spina bifida, is now accepted [174-176]. Within the first month of conception, the neural tube closes and if this closure is incomplete, this leads to NTDs [177], with folic acid thought to be essential in this process. As a result the UK Department of Health recommended in 1992, that females intending to become pregnant should increase their intake of folate by an additional 400 mcg daily from preconception until 12 weeks of gestation to be accomplished through the increased consumption of folate rich foods and/or taking a supplement delivering 400 mcg folic acid, with the latter emphasised as the most important [178].

A 2009 study sought to examine the success of this recommendation in an inner city setting [179] in pregnant women in their first trimester. Whereas 76% of the cohort reported consuming supplements containing the vitamin throughout the first trimester of pregnancy, only 12% commenced preconception, and only 17% started use before neural tube closure. This situation was similarly reflected in a later UK study in 466,860 females who had attended antenatal screening for NTDs and Down's syndrome [180]. The proportion of those women optimising their diet with the vitamin in supplement form before pregnancy reduced to 31% in 2011-2012 from 35% in 1999-2001. Of women aged below 20, only 6% used supplements containing folic acid prior to pregnancy, in comparison to 40% of those aged 35-39, with significant social and cultural differences also identified. Of those females who had previously experienced an NTD pregnancy, before their current pregnancy, only 51% reported taking folic acid supplements.

A 2016 UK study investigated the prevalence of pregnancies with NTDs and attempted to quantify those incidences that might have been preventable had fortification of folic acid been pursued [155]. It concluded that in the two decades from found that from 1991, the incidence of NTD pregnancies was 1.28 per 1000 total births. This was characterised by 81% terminations, 19% live births, with 0.5% stillbirths and fetal deaths at 20 weeks or more gestation. It estimated in UK, had the fortification of folic acid been followed at levels recommended in USA from 1998 onwards, around 2014 less NTD pregnancies might have resulted and concludes "failure to implement folic acid fortification in the UK has caused, and continues to cause, avoidable terminations of pregnancy, stillbirths, neonatal deaths and permanent serious disability in surviving children".

A 2015 meta-analysis and systematic review of UK data assessed the risk of neonates being small for gestational age according to the timing of initiation of folic acid supplementation. It identified that of the pregnancies where folic acid supplementation was recorded, when it was initiated before conception in 25.5% of cases. It concluded, supplementation significantly reduces the risk of small-for-gestational age at birth, but only if commenced pre-conceptually [181].

CONCLUSION

Literature from as far back as the 1970s clearly demonstrates that OCs induce depletions of a number of vitamins, minerals and other nutrients. More recent data suggests a negative impact of OCs upon vitamin B6, folate, vitamin B12, zinc, selenium, magnesium [13,48-50,54,65,67], even when lower dose formulations are taken into consideration. In UK, the most recent National Diet and Nutrition Survey published in January 2019, indicates little has changed in terms of improvement in the nutritional status of females of a child bearing age, with folate intake reducing by 5 mcg/day during the latest period under review, in this cohort and with a similarly low consumption of foods rich in vitamin B12, magnesium, selenium and zinc as in the previous report [182].

As already highlighted, there are significant numbers of women of childbearing age with an inadequate intake of folic acid in the UK, along with considerable variation in attitudes to pre-conceptual use of supplements containing the vitamin. Furthermore, given the high rate of unplanned pregnancies whilst females are taking OCs, as well as the likelihood that any pregnancy which might occur within 3 months of discontinuing the drug could do so in a state of a less than optimal folate status, it would appear that folic acid supplementation is the minimal intervention that might be considered for users of OCs, especially in countries which do not implement fortification of foods, such as UK. There are still around 1000 pregnancies with a diagnosis of NTD occurring in UK and around 80% of these ending in termination [183] and it is highly possible that an improved level of compliance with folic acid supplementation concurrent with OC usage would more than likely impact positively on this unsatisfactory situation.

From the preceding review it would appear the optimal dietary supplement to be taken alongside OCs, irrelevant of

their pharmacology, should contain B complex vitamins, together with folic acid, vitamins B12, C and E along with minerals, including zinc, magnesium, and selenium. Finally, it is highly likely that many women who use OCs throughout their reproductive years, may then go on to possibly be exposed to ongoing levels of the same exogenous hormone sources should they engage with Hormone Replacement Therapy as they enter the peri-menopause and subsequently experience the menopause. As a result, it follows that without adequate supplementation, these women are likely to have been, and continue to be exposed to possibly decades of a less than optimal status of one or more of the nutrients discussed above, with unknown potential long-term consequences.

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