A Review of the effects of oral contraceptives on nutrient status, with especial consideration to folate in UK

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 malabsorption 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 strategyin 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 Ethinylestradiol (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 20mcg 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). OCs can affect nutrient status via a number of different mechanisms dependent upon the micronutrient involved. These can include either/or reduction in absorption, increased excretion, inhibited conversion to active form, altered distribution in the body, modified metabolism or a combination of one or more of these factors.This review seeks to establish the extent to which OCs might impact upon micronutrient status of users and identify potential consequences of these effects.

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 within the primary research were also examined.

Results

Vitamin A

It is suggested that oestrogens 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 thethiamine-dependent enzyme-erythrocyte-transketolaseis somewhat reduced, possibly resulting in possible thiamine deficiency, whilst others do not concur (17-20).

One study in women using 500mcg dl-norgestrel and 50mcg EE examined the additional needs of thiamine, pyridoxine and riboflavin required to stabilise their status (21). It wasfound that daily supplementation with 2mg riboflavin and 3mg thiamine mitigated any declines in nutritional status, whilst pyridoxine at a daily dose of 10mg 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). Deficienciesof 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 oestrogen 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) (15,27-4) 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 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 (44). They also reported that the rate of decrease in mean serum folate levels increased with longer duration of use of OCs, but within 3 monthsof 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).In2012, 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 mightenhance 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 (56,43). In a later study,OCconsumption was found to be

associated with reducedconcentrations 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 oestrogen 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 malabsorption pathologies occur (57). Recently, in women taking low-dose OCs, it was reported that compared to controls the former group experienced significantly elevatedlevels of malondialdehyde levels in the plasma, which were associated with a reduction in glutathione peroxidase and reductaseezymes and indicative of increased oxidative stress (71). However, supplementation with vitamins C and E significantly reversed these changes (71).It is possible that oestrogens 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 oestrogens (17,72,73).

Vitamin E

The administration of contraceptive steroids in preclinical models, reducedlevels of plasma tocopherol levels, significantly, andalso 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 plateletclotting activity in conjunction with a reduction in vitamin E plasma levels in OC users which was reversed with administration of the vitamin (77).

Magnesium

Oestrogens 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). Oestrogen therapy, whether through use of OCs or Hormone replacement therapy(HRT), reduceslevels 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 (79,81,82-85). 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 hypomagnesemiamight be associated with thromboembolic side effects associated with oestrogens (78,79).

Zinc

50 years ago, lower levels of zinc were identified in the plasma ofOC 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 oestrogen 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, injectables 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 perimenopause 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 < 800mg/d (111).

Copper

A recent meta-analysis demonstrates even the more recently developed OCs containing, EE doses of 25-30mcg 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 ofcontraceptive users, serum levels of α-tocopheroland 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-tocopheroland coenzyme Q 10 (114). Oestrogen 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 identifiedOCs 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 vitaminsB6, B12 and folate were used to examine the relationship between depression in women who used OCs, (129). OC users were reported to more depressed 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 metabolismof leptinand 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 Econferenhanced 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 vitaminsC 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 (748nmol/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 an 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, who 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=1mcg food folate or 600mcg 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 aMTHFR TT genotype to be associated with lowered serum folate levels, increased plasma homocysteineas 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 resultthe 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 accomplishedthrough the increased consumption of folate rich foods and/or taking a supplement delivering 400mcg 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 preventablehad 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 foetal 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 preconceptually (181).

Conclusions

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 5mcg/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 preconceptual 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.Whilst not all studies support this conjecture (184) one population based case control study in China found amongst other factors, exposure to oral contraceptive use (adjusted OR 2.06, 95%CI1.16, 3.68) to be significantly associated with NTDs (185). Furthermore, the number of predicted NTD cases declined by 23.7% to 31.4%- depending on median baseline folate levels- in women taking a folic acid fortified OC compared with taking a traditional OC leading the authors to conclude the strategy has the potential to reduce the number of folate-dependent NTDs among current and recent OC users (186). This has led one group to suggest (187) "Information on the beneficial effects of folic acid or folic acid containing multivitamins could and should be provided on the contraceptive packet. Thus our hope is that the user of this medicinal product will have better knowledge to understand that the start of the use of folic acid or multivitamins immediately after the discontinuation of oral contraceptive pills is necessary when couples decide to have a baby."

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, includingzinc, 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 perimenopause 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.

References

1. Brunton L L, Blumenthal D, Murri N, Dandan R, Knollmann B. In: Goodman & Gilman's ThePharmacological Basis of Therapeutics. XII ed.New York; 2011.
2. Lobo R, Stanczyk F. New knowledge in the physiology of hormonal contraceptives. Am J ObstetGynecol 1994; 170: 1499-1507.
3. Shulman LP. The state of hormonal contraception today: benefits and risks of hormonal contraceptives: combined estrogen and progestin contraceptives. Am J ObstetGynecol 2011; 205: S9-13.
4. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. Eur J ContraceptReprod Health Care 2010; 15(Suppl 2): S19-31.
5. Bitzer J, Simon J. Current issues and available options in combined hormonal contraception. Contraception 2011; 84: 342-356.
6. Gallo M, Nanda K, Grimes D, Lopez L, Schulz K. 20 microg versus >20 microgestrogen combined oral contraceptives for contraception. Cochrane Database Syst Rev 2011; (1): CD003989.
7. Theuer RC. Effect of Oral Contraceptive Agents on Vitamin and Mineral Needs: A Review. J Reprod Med. 1972;8:13-19.
8. Berg G, Kohlmeier L, Brenner H. Effect of Oral Contraceptive Progestins on Serum Copper Concentration. Eur J ClinNutr. 1998;52:711-715.
9. Ghayour-Mobarhan M, Taylor A, New SA, Lamb DJ, Ferns GA. Determinants of Serum Copper, Zinc and Selenium in Healthy Subjects. Ann ClinBiochem. 2005;42:364-375.
10. Tamura T, Picciano MF. Folate and Human Reproduction. Am J ClinNutr 2006;83: 993-1016.
11. Prevention of Neural Tube Defects: Results of the Medical Research Council Vitamin Study. Mrc Vitamin Study Research Group. Lancet. 1991;338:131-137.
12. Prasad AS, Oberleas D, Moghissi KS, Stryker JC, Lei KY. Effect of Oral Contraceptive Agents on Nutrients: Ii. Vitamins. Am J ClinNutr. 1975;28:385-391.
13. Wilson SM, Bivins BN, Russell KA, Bailey LB. Oral Contraceptive Use: Impact on Folate, Vitamin B(6), and Vitamin B(1)(2) Status. Nutr Rev. 2011;69:572-583.
14. Mooij PN, Thomas CM, Doesburg WH, Eskes TK. Multivitamin supplementation in oral contraceptive users. Contraception 1991;44:277-288.
15. Tyrer LB. Nutrition and the pill. J Reprod Med 1984;29:547-550.
16. Ahmed F, Bamji MS, Iyengar L. Effect of oral contraceptive agents on vitamin nutrition status. Am J ClinNutr 1975;28:606-615
17. Thorp VJ. Effect of oral contraceptive agents on vitamin and mineral requirements. J Am Diet Assoc 1980;76:581-584.
18. Briggs MH, Briggs M. Thiamine status and oral contraceptives. Contraception. 1975 Feb 1;11(2):151-154.

19. Vir SC, Love AH. Effect of oral contraceptive agents on thiamin status. International journal for vitamin and nutrition research. InternationaleZeitschrift fur Vitamin-und Ernahrungsforschung. Journal international de vitaminologie et de nutrition. 1979;49(3):291-295.
20. Lewis CM, King JC. Effect of oral contraceptives agents on thiamin, riboflavin, and pantothenic acid status in young women. The American journal of clinical nutrition. 1980 Apr 1;33(4):832-838.
21. Ahmed F, Bamji MS. Vitamin supplements to women using oral contraceptives (studies of vitamins B1, B2, B6 and A). Contraception. 1976 Sep 1;14(3):309-318.
22. Newman LJ, Lopez R, Cole HS, Boria MC, Cooperman JM. Riboflavin deficiency in women taking oral contraceptive agents. The American journal of clinical nutrition. 1978 Feb 1;31(2):247-249.
23. Sanpitak N, Chayutimonkul L. Oral contraceptives and riboflavine nutrition. Lancet 1974; 1: 836-837.
24. Bamji M, Prema K, Jacob C, Rani M, Samyukta D. Vitamin supplements to Indian women using low dosage oral contraceptives. Contraception 1985; 32: 405-416
25. Roe DA, Bogusz S, Sheu J, McCormick DB. Factors affecting riboflavin requirements of oral contraceptive users and nonusers. The American journal of clinical nutrition. 1982 Mar 1;35(3):495-501.
26. Zencirci B. Comparison of the effects of dietary factors in the management and prophylaxis of migraine. J Pain Res 2010; 3: 125-130.
27. Matsui MS, Rozovski SJ. Drug-nutrient interaction. ClinTher 1982;4:423-440.
28. Prasad AS, Lei KY, Moghissi KS, et al. Effect of oral contraceptives on nutrients. III. Vitamins B6, B12 and folic acid. Am J ObstetGynecol 1976;125:1063-1069.
29. Butterworth CE. Interactions of nutrients with oral contraceptives and other drugs J Am Diet Assoc 1973;62:510-4
30. Haspels AA, Bennink HJ, Schreurs WH. Disturbance of tryptophan metabolism and its correction during oestrogen treatment in postmenopausal women. Maturitas 1978;1:15-20.
31. Rose D P. The influence of oestrogens on tryptophan metabolism in man. ClinSci 1966; 31: 265- 272.
32. Lussana F, Zighetti Ml, Bucciarelli P, Cugno M, Cattane M. Blood levels of homocysteine, folate, vitamin B6 and B12 in women using oral contraceptives compared to non-users. Thromb Res 2003; 112: 37-41.
33. Lumeng L, Cleary Re, Li Tk. Effect of oral contraceptives on the plasma concentration of pyridoxal phosphate. Am J ClinNutr 1974; 27: 326-333.
34. Morris Ms, Picciano Mf, Jacques Pf, Selhub J. Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003-2004. Am J ClinNutr 2008; 87: 1446-1454.
35. Leklem Je, Brown Rr, Rose Dp, Linkswiler Hm. Vitamin B6 requirements of women using oral contraceptives. Am J ClinNutr 1975; 28: 535-541.
36. Leklem Je. Vitamin B-6 requirement and oral contraceptive use--a concern? J Nutr 1986; 116: 475- 477.
37. van der Vange N, van der Berg H, Kloosterboer HJ, Haspels AA. Effects of seven low-dose combined contraceptives on vitamin B6 status. Contraception 1989;40:377-84..
38. Miller, L T Do oral contraceptive agents affect nutrient requirements--vitamin B-6? The Journal of nutrition, July 1986, Vol.116(7), pp.1344-1345
39. Trowbridge M, Jr., Wadsworth R, Moffitt E. Malabsorption associated with gluten enteropathy, do oral contraceptives interfere with folate metabolism? J Maine Med Assoc 1968; 59: 240-242.
40. Paton A. Oral contraceptives and folate deficiency. Lancet 1969; 1: 418.
41. Ryser J, Farquet J, Petite J. Megaloblasticanemia due to folic acid deficiency in a young woman on oral contraceptives. ActaHaematol 1971; 45: 319-324.
42. Whitehead N, Reyner F, Lindenbaum J. Megaloblastic changes in the cervical epithelium. Association with oral contraceptive therapy and reversal with folic acid. JAMA 1973; 226: 1421-1424
43. Shojania AM. Oral contraceptives: effect of folate and vitamin B12 metabolism. Can Med Assoc J 1982; 126: 244-247
44. Shojania A M, Hornady G, Barnes P. Oral contraceptives and serum-folate level. Lancet 1968; 1: 1376-1377.
45. Pritchard J, Scott D, Whalley P. Maternal folate deficiency and pregnancy wastage. IV. Effects of folic acid supplements, anticonvulsants, and oral contraceptives. Am J ObstetGynecol 1971; 109: 341-346.
46. Castren O M, Rossi R R. Effect of oral contraceptives on serum folic acid content. J ObstetGynaecol Br Commonw 1970; 77: 548-550.
47. Green T, Houghton L, Donovan U, Gibson R, O'connor D. Oral contraceptives did not affect biochemical folate indexes and homocysteine concentrations in adolescent females. J Am Diet Assoc 1998; 98: 49-55.
48. Shere M, Bapat P, Nickel C, Kapur B, Koren G. Association between use of oral contraceptives and folate status: a systematic review and meta-analysis. Journal of Obstetrics and Gynaecology Canada. 2015 May 1;37(5):430-8.
49. Castano PM, Aydemir A, Sampson-Landers C, Lynen R. The folate status of reproductive-aged women in a randomised trial of a folate-fortified oral contraceptive: dietary and blood assessments. Public health nutrition. 2014 Jun;17(6):1375-1383.
50. Fruzzetti, F. Beyaz P An oral contraceptive fortified with folate Women's Health 8.1 (Jan 2012): 13-9.
51. Butterworth CE, Hatch KD, Gore H, et al. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. Am J ClinNutr 1982;35:73-82.
52. Check WA. Folate for oral contraceptive users may reduce cervical cancer risk. J Am Med Assoc 1980;244:633-4.
53. Wertalik L, Metz E, Lobuglio A, Balcerzak S. Decreased Serum B 12 Levels With Oral ContraceptiveUse. Jama 1972; 221: 1371-1374.

54. Sutterlin M, Bussen S, Rieger L, Dietl J, Steck T. Serum Folate And Vitamin B12 Levels In WomenUsing Modern Oral Contraceptives (Oc) Containing20 MicrogEthinylEstradiol. Eur J ObstetGynecolReprodBiol 2003; 107: 57-61.
55. Riedel B, BjorkeMonsen A, Ueland P, Schneede J. Effects Of Oral Contraceptives And Hormone ReplacementTherapy On Markers Of Cobalamin Status.ClinChem 2005; 51: 778-781.
56. Shojania Am, Wylie B. The Effect Of Oral Contraceptives On Vitamin B12 Metabolism. Am J ObstetGynecol 1979; 135: 129-134.
57. Veninga K S. Effects Of Oral Contraceptives On Vitamins B6, B12, C, And Folacin. J Nurse Midwifery 1984; 29: 386-390.
58. Hielt K, Brynskov J, Hippe E, et al. Oral contraceptives and the cobalamin (vitamin B12) metabolism. ActaObstetGynecolScand 1985;64:59-63.
59. Grace E, Emans SJ, Drum DE. Hematologic abnormalities in adolescents who take oral contraceptive pills. J Pediatrics 1982;101:771-774
60. Barone C, Bartoloni C, Ghirlanda G, Gentiloni N. Megaloblasticanemia due to folic acid deficiency after oral contraceptives. Haematologica 1979;64:190-195.
61. McArthur J O. Biological Variability and Impact of Oral Contraceptives on Vitamins B6, B12 and Folate Status in Women of Reproductive Age .Nutrients 2013, 5, 3634-3645
62. Adams MJ Jr, Khoury MJ, Scanlon KS, Stevenson RE, Knight GJ, Haddow JE et al. Elevated Midtrimester Serum Methylmalonic Acid Levels as a Risk Factor for Neural Tube Defects. Teratology. 1995;51:311-317.
63. Gardyn J, Mittelman M, Zlotnik J, Sela BA, Cohen AM. Oral Contraceptives Can Cause Falsely Low Vitamin B(12) Levels. ActaHaematol. 2000;104:22-24
64. Bush A I. The Metallobiology of Alzheimer's Disease. Trends Neurosci. 2003;26: 207-214
65. Dante G et al. Vitamin and mineral needs during the oral contraceptive therapy: a systematic review. Int J ReprodContraceptObstet Gynecol. 2014 Mar;3(1):1-10
66. Basnayake S, de Silva SV, Miller PC, Rogers S. A Trial of Daily Vitamin Supplementation as a Means of Reducing Oral Contraceptive Side Effects and Discontinuation in Sri Lanka. Contraception. 1983;27:465-472
67. Palmery, A. Saraceno, A. Vaiarelli, G. Carlomagno Oral contraceptives and changes in nutritional requirements European Review for Medical and Pharmacological Sciences 2013; 1804-1812
68. Webb JL. Nutritional effects of oral contraceptive use: a review. J Reprod Med 1980; 25: 150-156.
69. WHO. Advances in Methods on Fertility Regulation. World Health Organization, 1975.
70. Hudiburgh N, Milner A. Influence of oral contraceptives on ascorbic acid and triglyceride status. J Am Diet Assoc 1979; 75: 19-22.
71. Zal F, Mostafavi-Pour Z, Amini F, Heidari A. Effect of vitamin E and C supplements on lipid peroxidation and GSH-dependent antioxidant enzyme status in the blood of women consuming oral contraceptives. Contraception 2012; 86: 62-66.
72. Weininger J, King JC. Effect of oral contraceptives on ascorbic acid status of young women consuming a constant diet. Nutr Rep Int 1977;15:255-264
73. Vihtamaki T, Parantainen J, Koivisto AM, et al. Oral ascorbic acid increases plasma oestradiol during postmenopausal hormone replacement therapy. Maturitas 2002;42:129-135
74. Aftergood L, Alfin-Slater R B. Oral contraceptive alpha- tocopherol interrelationships. Lipids 1974; 9: 91-96.
75. Akinsanya M, Adeniyi T, Ajayi G, Oyedele M. Effects of vitamin E and folic acid on some antioxidant enzymes activities of female Wistar rats administered combined oral contraceptives. African J Biochem Res 2010; 4: 238-242.
76. Brigg M. Letter: vitamin E status and oral contraceptives. Am J ClinNutr 1975; 28: 436.
77. Renaud S, Ciavatti M, Perrot L, Berthezene F, Dargent D, Condamin P. Influence of vitamin E administration on platelet functions in hormonal contraceptive users. Contraception 1987; 36: 347-358.
78. Seelig MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. Magnes Res 1990;3:197-215
79. Seelig MS. Interrelationship of magnesium and estrogen in cardiovascular and bone disorders, eclampsia, migraine, and premenstrual syndrome. J Am CollNutr 1993;12:442-458
80. Muneyyirci-Delale O, Nacharaju VL, Dalloul M, et al. Serum ionized magnesium and calcium in women after menopause: inverse relation of estrogen with ionized magnesium. FertilSteril 1999;71:869-872.
81. Stanton MF, Lowenstein FW. Serum magnesium in women during pregnancy, while taking contraceptives, and after menopause. J Am CollNutr 1987;6:313-319
82. Akinloye O, Adebayo T, Oguntibeju O, Oparinde D, Ogunyemi E. Effects of contraceptives on serum trace elements, calcium and phosphorus levels.West Indian Med J 2011; 60: 308-315.
83. Hameed A, Majeed T, Rauf S, Ashraf M, Jalil M, Nasrullah M, Hussan A, Noreen R. Effect of oraland injectable contraceptives on serum calcium,magnesium and phosphorus in women. J AyubMed Coll Abbottabad 2001; 13: 24-25.
84. Olatunbosun D, Adeniyi F, Adadevoh BK. Effect of oral contraceptives on Serum magnesium levels. Int J Fertil 1974; 19: 224-226.
85. Blum M, Kitai E, Ariel Y, Schnierer M, Bograd H. Oral contraceptive lowers serum magnesium. Harefuah 1991; 121: 363-364.
86. Cowan JA. Introduction to the biological chemistry of magnesium. ed. J.A. Cowan. New York. VCH;1995.

87. Halsted JA, Hackley BM, Smith JC, Jr. Plasma-zinc and copper in pregnancy and after oral contraceptives. Lancet 1968; 2: 278-279
88. King JC. Do women using oral contraceptive agents require extra zinc? J Nutr 1987; 117: 217- 219
89. Briggs Mh, Briggs M, Austin J. Effects of steroid pharmaceuticals on plasma zinc. Nature 1971; 232: 480-481
90. Prema K, Ramalakshmi Ba, Babu S. Serum copper and zinc in hormonal contraceptive users. FertilSteril 1980; 33: 267-271.
91. Fallah S, SaniFv, Firoozrai M. Effect of contraceptive pill on the selenium and zinc status of healthy subjects. Contraception 2009; 80: 40-43.
92. Chilvers DC, Jones MM, Selby PL, et al. Effects of oral ethinyloestradiol and norethisterone on plasma copper and zinc complexes in post-menopausal women. Hormone Metab Res 1985;17:532-535.
93. Smith JC, Brown ED. Effects of oral contraceptive agents on trace element metabolism - a review. In: Prasad AS (ed). Trace Elements in Human Health and Disease. Vol.II, Essential and Toxic Elements. New York: Academic Press, 1976. 315-345.
94. Vir SC, Love AH. Zinc and copper nutriture of women taking oral contraceptive agents. Am J ClinNutr 1981;34:1479-1483
95. Hinks LJ, Clayton BE, Lloyd RS. Zinc and copper concentrations in leukocytes and erythrocytes in healthy adults and the effect of oral contraceptives. J ClinPathol 1983;36:1016-1021.
96. Powell-Beard L, Lei KY, Shenker L. Effect of long-term oral contraceptive therapy before pregnancy on maternal and fetal zinc and copper status. ObstetGynecol 1987;69:26-32.
97. Liukko P, Erkkola R, Pakarinen P, et al. Trace elements during 2 years' oral contraception with low-estrogen preparations. GynecolObstet Invest 1988;25:113-117.
98. Thane, C W et al : Oral contraceptives and nutritional status in adolescent British girls. Nutrition Research, 2002, 22, 449-462
99. Gambacciani, M.; Cappagli, B.; Lazzarini, V.; Ciaponi, M.; Fruzzetti, F.; Genazzani, A.R. Longitudinal evaluation of perimenopausal bone loss: Effects of different low dose oral contraceptive preparations on bone mineral density. Maturitas2006, 54, 176–180
100. Kleerekoper, M.; Brienza, R.S.; Schultz, L.R.; Johnson, C.C. Oral contraceptive use may protect against low bone mass. Henry Ford Hospital Osteoporosis Cooperative Research Group. Arch. Intern. Med. 1991, 151, 1971–1976.
101. Kuohung, W.; Borgatta, L.; Stubblefield, P. Low-dose oral contraceptives and bone mineral density: An evidence-based analysis. Contraception 2000, 61, 77–82.
102. Liu, S.L.; Lebrun, C.M. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: A systematic review. Br. J. SportsMed. 2006, 40, 11–24.
103. Garnero, P.; Sornay-Rendu, E.; Delmas, P.D. Decreased bone turnover in oral contraceptive users. Bone 1995, 16, 499–503.
104. Zittermann, A. Decreased urinary calcium loss and lower bone turnover in young oral contraceptive users. Metabolism.2000, 49, 1078–1082
105. Goulding, A.; McChesney, R. Oestrogen-progestogen oral contraceptives and urinary calcium excretion. Clin. Endocrinol. 1977, 6, 449–454.
106. Hartard, M.; Kleinmond, C.; Kirchbichler, A.; Jeschke, D.; Wiseman, M.; Weissenbacher, E.R.; Felsenberg, D.; Erben, R.G. Age at first oral contraceptive use as a major determinant of vertebral bone mass in female endurance athletes. Bone 2004, 35, 836–841.
107. Cobb, K.L.; Kelsey, J.L.; Sidney, S.; Ettinger, B.; Lewis, C.E. Oral contraceptives and bone mineral density in white and black women in CARDIA. Coronary Risk Development in Young Adults. Osteoporos. Int. 2002, 13, 893–900.
108. Hartard, M.; Bottermann, P.; Bartenstein, P.; Jeschke, D.; Schwaiger, M. Effects on bone mineral density of low-dosed oral contraceptives compared to and combined with physical activity. Contraception 1997, 55, 87–90.
109. Burr, D.B.; Yoshikawa, T.; Teegarden, D.; Lyle, R.; McCabe, G.; McCabe, L.D.; Weaver, C.M. Exercise and oral contraceptive use suppress the normal age-related increase in bone mass and strength of the femoral neck in women 18-31 years of age. Bone 2000, 27, 855–863.
110. Weaver, C.M.; Teegarden, D.; Lyle, R.M.; McCabe, G.P.; McCabe, L.D.; Proulx, W.; Kern, M.; Sedlock, D.; Anderson, D.D.; Hillberry, B.M.; et al. Impact of exercise on bone health and contraindication of oral contraceptive use in young women. Med. Sci. Sports Exerc. 2001, 33, 873–880.
111. Teegarden, D.; Legowski, P.; Gunther, C.W.; McCabe, G.P.; Peacock, M.; Lyle, R.M. Dietary calcium intake protects women consuming oral contraceptives from spine and hip bone loss. J. Clin. Endocrinol. Metab. 2005, 90, 5127–5133.
112. Babić Z, Tariba B, Kovačić J, Pizent A, Varnai V, Macan J. Relevance of serum copper elevation induced by oral contraceptives: a meta-analysis Contraception 87 (2013) 790–800
113. Prabhudas R. Palan, Felix Strube, JurajLetko, AzraSadikovic, andMagdyS.Mikhail Effects of Oral, Vaginal, and Transdermal Hormonal Contraception on Serum Levels of Coenzyme Q10, Vitamin E, and Total Antioxidant Activity Obstetrics and Gynecology International Volume 2010, Article ID 925635, 4 pages doi:10.1155/2010/925635
114. P. R. Palan, K. Connell, E. Ramirez et al. Effects of menopause and hormone replacement therapy on serum levels of coenzyme Q10 and other lipid-soluble antioxidants.Biofactors. 2005;25(1-4):61-6.

115. Knopp RH, Zhu X, Bonet B. Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. Atherosclerosis. 1994 Oct 1;110:S83-91
116. Palan PR, Romney SL, Vermund SH, Mikhail MG, Basu J. Effects of smoking and oral contraception on plasma β-carotene levels in healthy women. American Journal of Obstetrics &Gynecology. 1989 Oct 1;161(4):881-885.
117. United Nations Department of Economic & Social Affairs, Population Division. World contraceptive use, 2012 : www.un.org/esa/ population/publications/contraceptive2011/wallchart_front.pdf
118. World Health Organization Department of Reproductive Health and Research (WHO/RHR), Johns Hopkins Bloomberg School of Public Health Center for Communication Programs (CCP), Knowledge for health project. Family planning: A global handbook for providers(2011 update) . Baltimore and Geneva: CCP and WHO 2011 ; 388 .
119. Office for National Statistics. Opinions Survey Report No. 41. Contraception and Sexual Health, 2008/09.
120. Rashed, A. 2013. Trends and patterns of hormonal contraceptive prescribing for adolescents in primary care in the UK. King's College London.
121. http://www.theguardian.com/society/2010/dec/03/hormone-implants-contraception-condoms
122. http://informahealthcare.com/doi/pdf/10.1080/13625180410001715681
123. Singh S, Sedgh G, Hussain R. Unintended pregnancy: Worldwide levels, trends, and outcomes .Stud FamPlann2010 ; 41(4) : 241 – 250
124. Khosravi A, Najafi F , Rahbar M R, e t a l. Health indicators in I.R. Iran . Tehran: Ministry of Health and Medical Education 2009 .http://behdasht.gov.ir/uploads/291_1041_simayeisalamat. Pdf
125. MoosazadehM ,Nekoei-Moghadam M , Emrani Z , Amiresmaili M . Prevalence of unwanted pregnancy in Iran: A systematic review and meta-analysis .Int J HealthPlann Manage 2014 ; 29(3) : 277 – 290 .
126. Ali MM, Cleland J G, Shah I H. Causes and consequences of contraceptive discontinuation: Evidence from 60 demographicand health surveys .Cairo: WHO 2012 .
127. Ponce de Leon R, Juarez-Perez MA, GrubbGS .Effect of vitamin B6 on the side effects of a low-dose combined oral contraceptive .Contraception1997 ; 55(4) : 245 –248 .
128. Mohammad-Alizadeh-Charandabi S , Mirghafourvand M, Froghy L, Javadzadeh Y, Razmaraii N. The effect of multivitamin supplements on continuation rate and side effects of combined oralcontraceptives: A randomised controlled trial. The European Journal of Contraception and Reproductive Health Care, 2015; 20: 361–371
129. Zolfaghari S.S. The Relationship Between Folic Acid, Vitamin B12, And Vitamin B6 Intakes And Depression In Women Who Use Hormonal Oral Contraceptives Thesis Presented to the Department of Family and Consumer Sciences California State University, Long Beach B.S., 2005, University of California, Irvine December 2015 ProQuest Number: 1604887
130. Westhoff CL, Heartwell S, Edwards S, Zieman M, Stuart G, Cwiak C, et al. Oral contraceptive discontinuation: do side effects matter? American Journal of Obstetrics and Gynecology. 2007; 196(4):412. e1- e7. PMID: 17403440
131. Oakley D, Sereika S, Bogue E-L. Oral contraceptive pill use after an initial visit to a family planning clinic. Family Planning Perspectives. 1991:150–154.
132. Rosenberg MJ, Waugh MS, Meehan TE. Use and misuse of oral contraceptives: risk indicators for poor pill taking and discontinuation. Contraception. 1995; 51(5):283–288.
133. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. American Journal of Obstetrics and Gynecology. 1998; 179(3):577–82. PMID: 9757954
134. Berenson AB, Rahman M. Changes in weight, total fat, percent body fat, and central-to-peripheral fat ratio associated with injectable and oral contraceptive use. American Journal of Obstetrics and Gynecology. 2009; 200(3):329. 1-8
135. De Melo N, Aldrighi J, Faggion D, Reyes V, Souza J, Fernandes C, et al. A prospective open-label study to evaluate the effects of the oral contraceptive Harmonet1(gestodene75/EE20) on body fat. Contraception. 2004; 70(1):65–71.
136. Gallo M, Lopez L, Grimes D, Schulz K, Helmerhorst F. Combination contraceptives: effects on weight (Review). Cochrane Database of Systematic Reviews. 2014;(1:):78.
137. Picardo CM, Nichols M, Edelman A, Jensen JT. Women's knowledge and sources of information on the risks and benefits of oral contraception. Journal of the American Medical Women's Association (1972). 2002; 58(2):112–116.
138. García OP, Long KZ, Rosado JL. Impact of micronutrient deficiencies on obesity. Nutrition Reviews. 2009; 67(10):559–572
139. Aasheim ET, Hofsø D, Hjelmesæth J, Birkeland KI, Bøhmer T. Vitamin status in morbidly obese patients: a cross-sectional study. The American Journal of Clinical Nutrition. 2008; 87(2):362–9. PMID: 18258626
140. Kimmons JE, Blanck HM, Tohill BC, Zhang J, Khan LK. Associations between body mass index and the prevalence of low micronutrient levels among US adults. Medscape General Medicine. 2006; 8 (4):59. PMID: 17415336
141. Park B, Kim J. Oral contraceptive use, micronutrient deficiency, and obesity among premenopausal females in Korea: The necessity of dietary supplements and food intake improvement. PloS one. 2016 Jun 27;11(6):e0158177.
142. Kowalska K, Milnerowicz H. Pro/antioxidant status in young healthy women using oral contraceptives Environmental Toxicology and Pharmacology 2016, 43: 1–6

143. Kamp F, Soares T, Rodrigues L, Donangelo C. Effect of oral contraceptive use and zinc supplementation on zinc, iron and copper biochemical indices in young women e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 6 (2011) 253-258
144. Bernstein P, Pohost G. Progesterone, progestins, and the heart. Rev Cardiovasc Med 2010;11:228-236.
145. Kiriwat O, Petyim S. The effects of transdermal contraception on lipid profiles, carbohydrate metabolism and coagulogram in Thai women. GynecolEndocrinol 2010;26:361-365.
146. Grigoryan OR, Grodnitskaya EE, Andreeva EN, Shestakova MV, Melnichenko GA, Dedov II. Contraception in perimenopausal women with diabetes mellitus. GynecolEndocrinol 2006;22:198- 206.
147. Minozzi M, Costantino D, Guaraldi C, Unfer V. The effect of a combination therapy with myo-inositol and a combined oral contraceptive pill versus a combined oral contraceptive pill alone on metabolic, endocrine, and clinical parameters in polycystic ovary syndrome. GynecolEndocrinol 2011;27:920-924.
148. Plu-Bureau G, Hugon-Rodin J, Maitrot-Mantelet L, Canonico M. Hormonal contraceptives and arterial disease: an epidemiological update. Best Pract Res ClinEndocrinolMetab 2013;27:35-45.
149. Dilbaz B, Ozdegirmenci O, Caliskan E, Dilbaz S, Haberal A. Effect of etonogestrel implant on serum lipids, liver function tests and hemoglobin levels. Contraception 2010;81:510-514.
150. Scharnagl H, Petersen G, Nauck M, Teichmann AT, Wieland H, Marz W. Double-blind, randomized study comparing the effects of two monophasic oral contraceptives containing ethinylestradiol (20 microg or 30 microg) and levonorgestrel (100 microg or 150 microg) on lipoprotein metabolism. Contraception 2004;69: 105-113.
151. Skouby SO, Endrikat J, Dusterberg B, Schmidt W, Gerlinger C, Wessel J, et al. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 microgethinylestradiol combined with 100 microglevonorgestrel. Contraception 2005;71:111-117.
152. Torkzahrani S, Heidari A, Mostafavi-pour Z, Ahmadi M, Zal F. Amelioration of lipid abnormalities by vitamin therapy in women using oral contraceptives. Clinical and experimental reproductive medicine. 2014 Mar 1;41(1):15-20.
153. NDNS. Results from Years 7-8 (combined) of the Rolling Programme (2014/2015 – 2015/16): UK Public Health England
154. Morris JK, Rankin J, Draper ES, Kurinczuk JJ, Springett A, Tucker D, Wellesley D, Wreyford B, Wald NJ. Prevention of neural tube defects in the UK: a missed opportunity. Archives of disease in childhood. 2016 Jul 1;101(7):604-607.
155. Lim U, Wang SS, Hartge P, Cozen W, Kelemen LE, Chanock S, Davis S, Blair A, Schenk M, Rothman N, Lan Q. Gene-nutrient interactions among determinants of folate and one-carbon metabolism on the risk of non-Hodgkin lymphoma: NCI-SEER case-control study. Blood. 2007 Apr 1;109(7):3050-3059.
156. Ogino S, Wilson RB. Genotype and haplotype distributions of MTHFR 677C> T and 1298A> C single nucleotide polymorphisms: a meta-analysis. Journal of human genetics. 2003 Jan;48(1):1.
157. Malinow MR, Nieto FJ, Kruger WD, Duell PB, Hess DL, Gluckman RA, Block PC, Holzgang CR, Anderson PH, Seltzer D, Upson B. The effects of folic acid supplementation on plasma total homocysteine are modulated by multivitamin use and methylenetetrahydrofolatereductase genotypes. Arteriosclerosis, thrombosis, and vascular biology. 1997 Jun 1;17(6):1157-1162.
158. Yang, Q.H., Botto, L.D., Gallagher, M., Friedman, J.M., Sanders, C.L., Koontz, D., Nikolova, S., Erickson, J.D. and Steinberg, K., 2008. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank–. *The American journal of clinical nutrition*, *88*(1), pp.232-246.
159. Yadav U, Kumar P, Yadav SK, Mishra OP, Rai V. Polymorphisms in folate metabolism genes as maternal risk factor for neural tube defects: an updated meta-analysis. Metab Brain Dis (2015) 30:7–24.
160. To QG, Chen TT, Magnussen CG, To KG. Workplace physical activity interventions: a systematic review. American Journal of Health Promotion. 2013 Jul;27(6):113-123.
161. Pfeiffer CM, Caudill SP, Gunter EW, Osterloh J, Sampson EJ. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999–2000. The American journal of clinical nutrition. 2005 Aug 1;82(2):442-450.
162. Hickling S, Hung J, Knuiman M, Jamrozik K, McQuillan B, Beilby J, Thompson P. Impact of voluntary folate fortification on plasma homocysteine and serum folate in Australia from 1995 to 2001: a population based cohort study. Journal of Epidemiology & Community Health. 2005 May 1;59(5):371-376.
163. Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. Teratology. 2002 Jul;66(1):33-39.
164. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, Fernandez B. Reduction in neural-tube defects after folic acid fortification in Canada. New England Journal of Medicine. 2007 Jul 12;357(2):135-142.
165. Mallard SR, Gray AR, Houghton LA. Periconceptional bread intakes indicate New Zealand's proposed mandatory folic acid fortification program may be outdated: results from a postpartum survey. BMC pregnancy and childbirth. 2012 Dec;12(1):8.

166. Yang QH, Carter HK, Mulinare J, Berry RJ, Friedman JM, Erickson JD. Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: findings from the National Health and Nutrition Examination Survey, 2001–2002–. The American journal of clinical nutrition. 2007 May 1;85(5):1409-1416.
167. Nagele P, Meissner K, Francis A, Födinger M, Saccone NL. Genetic and environmental determinants of plasma total homocysteine levels: impact of population-wide folate fortification. Pharmacogenetics and genomics. 2011 Jul;21(7):426.
168. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline (1998) Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. The National Academies Press, Washington DC
169. Solis C, Veenema K, Ivanov AA, Tran S, Li R, Wang W, Moriarty DJ, Maletz CV, Caudill MA. Folate intake at RDA levels is inadequate for Mexican American men with the methylenetetrahydrofolatereductase 677TT genotype. The Journal of nutrition. 2008 Jan 1;138(1):67-72.
170. Stamm RA, Houghton LA. Nutrient intake values for folate during pregnancy and lactation vary widely around the world. Nutrients. 2013 Sep 30;5(10):3920-3947.
171. Australian Government Department of Health Nutrient Reference Values (2006). http://www.nrv.gov.au/home
172. Clinical Guideline (2014) Vitamin and mineral supplementation in pregnancy. Policy developed by: SA Maternal and Neonatal Clinical Network. Govt of South Australia.Approved 19 Dec 2014. https://www.sahealth.sa.gov.au/wps/wcm/connect/f53d44004eee83bc8104a36a7ac0d6e4/Vitamin+mineral+supplementation_Clinical+Guideline_final_Dec14.pdf?MOD=AJPERES&CACHEID=f53d44004eee83bc8 104a36a7ac0d6e4
173. Colson N J, Naug H, Nikbakht E, Zhang P, McCormack The impact of MTHFR 677 C/T genotypes on folate status markers: a meta‐analysis of folic acid intervention studiesJEur J Nutr (2017) 56:247–260
174. MRC Vitamin study research group (1991) Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet338, 131–137.
175. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. New England journal of medicine. 1992 Dec 24;327(26):1832-1835.
176. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, Mulinare J, Zhao P, Wong LY, Gindler J, Hong SX. Prevention of neural-tube defects with folic acid in China. New England Journal of Medicine. 1999 Nov 11;341(20):1485-90.
177. Moore, K.L. &Persaud, T. (1998) Before We Are Born: Essentials of Embryology and Birth Defects. Philadelphia: WBSaunders Company
178. Department of health (1992) Folic Acid and the Prevention ofNeural Tube Defects. Report From an Expert Advisory Panel. London: HMSO.
179. Brough L, Rees G A, Crawford M A, Dorman E K. Social and ethnic differences in folic acid use during preconception and early pregnancy in the UK: effect on maternal folate status . The British Dietetic Association Ltd 2009 J Hum Nutr Diet, 22, pp. 100–107
180. Bestwick J P, Huttly W J, Morris J K, Wald N J. Prevention of Neural Tube Defects: A Cross-Sectional Study of the Uptake of Folic Acid Supplementation in Nearly Half a Million Women PLOS ONE | www.plosone.org 6 February 2014 | Volume 9 | Issue 2 | e89354
181. Hodgetts VA, Morris RK, Francis A, Gardosi J, Ismail KM. Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2015 Mar 1;122(4):478-90.
182. National Diet and Nutrition Survey: Years 1 to 9 of the Rolling Programme (2008/2009 – 2016/2017): Time trend and income analyses. Public Health England. Published January 2019 PHE publications gateway number: 2018756
183. Wald NJ, Morris JK, Blakemore C. Public health failure in the prevention of neural tube defects: time to abandon the tolerable upper intake level of folate. *Public Health Rev*. 2018;39:2. Published 2018 Jan 31. doi:10.1186/s40985-018-0079-6
184. Ericson A, Kallen B, Lofkist E. Environmental factors in the etiology of neural tube defects: A negative study. Environmental Research. 1988:45:38-47
185. Yin Z, Xu W, Xu C, Zhang S, Zheng Y, Wang W, Zhou B. A population-based case-control study of risk factors for neural tube defects in Shenyang, China. Childs NervSyst (2011) 27:149–154
186. Taylor TN, Farkouh RA, Graham JB, et al. Potential reduction in neural tube defects associated with use of Metafolin-fortified oral contraceptives in the United States. Am J ObstetGynecol 2011;205:460.1-8.
187. Czeizel A, Dudás I, Paput L, Bánhidy F Prevention of Neural-Tube Defects with Periconceptional Folic Acid, Methylfolate, or Multivitamins? Ann NutrMetab 2011;58:263–271