Nutrition Research Reviews (2017), **30**, 265–271
doi:10.1017/S0954422417000142

Folate status in women of childbearing age with obesity: a review

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Abstract

Several studies have described a positive association between elevated BMI and birth defects risk. Data on plasma concentration of folate in pregnant women with obesity have shown values far below those recommended, regardless of diet, while folate levels should increase before pregnancy to reduce neural tube defects. We report a descriptive review of the most recent studies (from 2005 to 2015) to evaluate folate status through a population of women of childbearing age affected by obesity. The literature contains few studies, which present conflicting results regarding folate status in non-pregnant women of childbearing age affected by obesity, and it appears that there is a modification in folate metabolism, with a reduction in plasma folate levels and an increase in erythrocyte folate uptake. In conclusion, the folate status in women of childbearing age should be assessed by both plasma and erythrocyte levels to start a personalised and more adequate supplementation before conception. Further studies need to be conducted in a larger population, which take into account variables that can affect folate metabolism, such as dietary intake, lifestyle and genetic factors, oral contraceptives or other drug use, previous weight-loss programmes, or a history of bariatric surgery.

Key words: **Folate status: Childbearing age: Women with obesity: Birth defects**

Introduction

Adequate dietary folate intake is essential for meeting the requirements for the functioning of the human body[1].

Neural tube defects (NTD), well-known consequences of folate deficiency, are the second most common cause of serious birth defects and affect 0·2–10 per 1000 established pregnancies worldwide. NTD result from a failure of the neural tube to close properly within 4 weeks following conception. There is a heavy burden of illness for both the mother and her offspring, with lifelong clinical and economic consequences, which may be prevented with adequate dietary folate intake[2]. In 1960s, the link between folate deficiency during pregnancy and fetal NTD emerged for the first time. Subsequently, it has been demonstrated that maintaining plasma folate levels >15·9 nmol/l and erythrocyte folate levels >906 nmol/l significantly reduces the incidence of NTD[3,4]. Similarly, the latest scientific evidence suggests that an erythrocyte folate concentration above 1000 nmol/l is required for optimal NTD prevention[2]. A recent meta-analysis also evaluated the impact of maternal plasma folate levels during pregnancy on DNA methylation in newborns, which identified differences between genes implicated in various developmental abnormalities other than NTD[5].

Folate is a water-soluble organic compound, which belongs to the group of B vitamins. It is an essential micronutrient for the synthesis of RNA and DNA for cell division and tissue growth, as well as for methylation reactions and amino acid metabolism[1,6].

A low plasma folate measurement is the earliest indicator of altered folate exposure because it reflects recent dietary intake (i.e. short-term status) and is highly responsive to intervention with folic acid. Erythrocyte folate is a sensitive indicator of long-term folate status, representing the amount of folate that accumulates in erythrocytes during erythropoiesis, thereby reflecting folate status during the preceding 120 d (i.e. the half-life of erythrocytes)[1].

Inadequate dietary intake of folate is one of the leading causes of folate deficiency[1]; other major causes include increased requirements due to pregnancy or neoplastic diseases, malabsorptive conditions, anti-folate drugs or other metabolic inhibitors, and alcohol intake (which affects both folate intake and absorption). Recent research indicates that exposure to UV light, including the use of tanning beds, can lead to a folate deficiency, particularly in vulnerable individuals, such as women who are pregnant or of childbearing age with high sun exposures[7].

In 2004, the National Health and Nutrition Examination Survey (NHANES) data found that increased BMI of women of childbearing age was associated with a lower plasma folate level[4]. Another study in a UK obstetric cohort found that lower folate concentrations were associated with higher BMI, independently from diet, age, BMI, vitamin supplements and parity[8].

Abbreviations: LBW, lean body weight; NTD, neural tube defects.

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However, data regarding folate status in women of childbearing age affected by overweight/obesity are scarce.

Several studies[9–11] have described a positive association between elevated BMI and risk of birth defects. Particularly, Rasmussen *et al.*[12] reported that maternal obesity was associated with a 1·7-fold increased risk of NTD and Carmichael *et al.*[9] suggested that pre-pregnancy obesity and low-quality diet (assessed by a fifty-eight-item FFQ) were both important and complex factors associated with an increased risk of several birth defects.

Data on plasma concentration of folate in pregnant women with obesity have shown values below those recommended, regardless of diet[8], and we know from authors like Mastroiacovo & Leoncini[13] that folate levels should be higher before pregnancy to decrease the risk of infants with NTD, low birth weight, preterm delivery and fetal growth retardation[14].

Therefore, it is important to understand how obesity may affect folate metabolism from the pre-conception period to pregnancy[15] and if this target needs specific recommendations to reduce adverse health outcomes in future generations.

Based on these considerations, the present review aims to report recently published research on this topic. We reviewed and summarised studies, published between 2005 and 2015, which assessed folate status in women of childbearing age (women between the ages of 15 and 49 years according to the WHO and Centers for Disease Control and Prevention (CDC))[16,17] with overweight/obesity.

We believe that a proper review on folate status of childbearing-age women with obesity will contribute to elucidate this important topic as well as raise awareness on the nutritional needs of women with obesity, from weight management before conception, to clinical practice guidelines targeted to address specific requirements for optimal nutrition in pregnancy through an adequate and attentive health policy.

Materials and methods

The search strategy was conducted to identify studies that examined the relationship between obesity and folic acid status in women of childbearing age.

We conducted a detailed literature search in English to identify all the studies performed from 2005 to 2015. The following electronic databases were searched: PubMed, Scopus, EMBASE and Web of Science.

The full electronic search strategy used was 'folic acid' OR 'folate' restricted to either 'Medical Subject Headings (MeSH®) major topic'/'Emtree term' of the article (PubMed and EMBASE, respectively) or restricted to 'Topic'/'Article title, Abstract, keywords' of the article (Web of Science and Scopus, respectively) AND 'obese women' restricted to title/abstract.

An initial search of English-language publications of the period 2005–2015, retrieved sixteen (PubMed), ten (Scopus), twelve (EMBASE) and twenty (Web of Science) titles and abstracts.

Studies that met the following criteria were included: (a) original study published in a peer-review journal; (b) studies conducted in the last 10 years; (c) case–control studies, cohort studies, randomised controlled trials, and meta-analyses; (d) women with obesity of childbearing age; and (e) reported data about concentration or metabolism of folate.

The exclusion criteria included duplicate studies, abstracts from unpublished studies, reviews, case reports, letters, studies without plasma concentration of folate, and studies on postmenopausal populations.

Results

According to our inclusion and exclusion criteria, we selected eight different studies (four case–control studies, one epidemiological study, one retrospective cohort study and two observational studies) conducted on women of childbearing age with obesity. We evaluated the possible relationship between obesity and folate deficiency and, as consequence, the risk of NTD during pregnancy.

The observational study conducted by Hirsch *et al.*[18] investigated whether there was an association between plasma folate and total homocysteine levels and the presence of non-alcoholic fatty liver disease in forty-three Chilean women, BMI $\geq 35\,kg/m^2$, and age range 25–53 years, before undergoing bariatric surgery and liver biopsy. For each patient, liver biopsies were graded for the presence of fat, inflammation and fibrosis on a scale from 0 to 3. Since the implementation of a national programme which replaced traditional flour in Chile with folic acid-fortified flour (200 µg folic acid per 100 g) in 2000, the study population showed plasma folate levels above the cut-off value (>6·8 nmol/l). However, the authors reported that mean plasma folate levels were significantly ($P=0·005$) lower in patients with severe non-alcoholic fatty liver disease (21·1 (SD 7·9) nmol/l) than in those with minimal or without liver damage (27·7 (SD 7·04) nmol/l). An inverse and significant correlation between plasma folate levels and BMI was observed (r –0·31; $P=0·046$).

In a case–control study conducted by Ortega *et al.*[19], the authors investigated the effect of two slightly hypoenergetic dietary interventions on plasma folate levels among sixty-seven Spanish young women (age range 20–35 years) with overweight/obesity. Folate and other nutrient intakes were assessed by means of a food diary kept over 3 d; particularly, folate intake was recorded in the form of dietary folate equivalents. Tobacco use, alcohol and folic acid supplementation and/or fortified food consumption were also investigated. At baseline, the mean folate intake was far below the recommended 400 µg/d according to the recommended daily intakes of energy and nutrients for the Spanish population[19]. Considering plasma folate levels at baseline, 1·6 % of the study population had plasma folate levels <6·8 nmol/l (high risk of folate deficiency cut-off value, as reported by Wartanowicz *et al.*[20]) and about 45 % of the sample <14·9 nmol/l (optimum status cut-off value, as reported by Wartanowicz *et al.*[20]). Additionally, only 62·1 % of the study population had plasma folate concentrations above ≥13·6 nmol/l, which was considered the lower limit of the range of plasma folate concentrations associated with very low risk for NTD, as reported by Sauberlich *et al.*[21]. No results were reported about the effect of tobacco use and alcohol consumption on folate levels while no significant differences were observed in the plasma baseline folate levels between those who had taken and those who had not taken supplements or fortified foods.

https://doi.org/10.1017/S0954422417000142 Published online by Cambridge University Press

Subsequently, Stern *et al.*[22] conducted a case–control study in order to compare pharmacokinetics of a single-dose folic acid supplementation in twelve women affected by obesity *v.* twelve normal-weight women of childbearing age (18–45 years old). At baseline, the study population reported plasma folate levels over the cut-off value (>15·9 nmol/l) and median plasma folate levels did not differ significantly ($P=0·94$) between women with or without obesity (median 21·6 (range 12·1–46·3) nmol/l and 23·1 (range 9·4–44·1) nmol/l, respectively). After oral folic acid supplementation (doses ranged from 0·0153 to 0·0917 mg/kg), plasma folate levels were assessed in the subsequent 10 h (0·5, 1, 2, 3, 4, 6, 8 and 10 h). Through statistical analysis, it was found that folic acid does not freely distribute into adipose tissue, probably secondary to its dependence on lean body weight (LBW). Individuals with obesity not only weigh more and have extra body fat, but they also have more lean mass. Consequently, peri-conceptional supplementation recommendations may need to be adjusted to account for LBW differences in the population with obesity due to its likely impact on folic acid pharmacokinetics.

Ruiz-Tovar *et al.*[23] performed a retrospective cohort study evaluating folate levels and other minerals and vitamins on thirty female patients with morbid obesity (mean age 47·7 SD 8·8) years; range 20–62 years) who had undergone a laparoscopic sleeve gastrectomy. These patients were assessed at baseline, and at 1, 3, 6, 9, 12, 18 and 24 months post-surgery. The authors reported mean plasma folate levels of 8·3 ng/ml. Folate deficiency occurred in only one patient (3·3 % of the study population).

The case–control study by Baltaci *et al.*[24] assessed plasma folate levels in 116 female subjects with obesity (mean age 37·7 (SD 9·1) years) and 103 aged-matched healthy lean women. The authors reported no significant difference in mean folate concentrations between women with or without obesity (8·9 (SD 6·7) pg/ml; 6·8 (SD 3·3) pg/ml, respectively; $P=0·06$) and between those with or without the metabolic syndrome (9·1 (SD 7·8) pg/ml; 8·4 (SD 3·9) pg/ml, respectively; $P>0·05$).

Tinker *et al.*[25] analysed the data from the National Health and Nutrition Examination Survey (NHANES), representative of the non-institutionalised civilian US population, to assess if BMI (normal-weight, overweight, and obesity categories) was associated with changes in the correlation between folic acid supplementation and folate status. The authors estimated the geometric mean concentration among non-pregnant women of childbearing age (4272 women, aged 15–44 years) of plasma folate (period 2003–2008), erythrocyte folate (period 2007–2008) and plasma total homocysteine (tHcy; period 2003–2006), adjusting for age, race and ethnicity, and total dietary folate for strata of supplement use and BMI (normal weight; overweight; obesity). The authors reported that BMI was inversely associated with plasma folate among women who did not use supplements containing folic acid. In fact, plasma folate levels were significantly lower in women with obesity rather than in women with BMI in the overweight or normal range (15·0, 16·0 and 16·4 ng/ml, respectively). Statistically, these significant differences in the adjusted geometric mean concentrations of plasma folate by BMI category were observed only among supplement non-users while in each BMI category, supplement non-users had significantly lower adjusted geometric mean concentrations of plasma folate than any category of supplement users. On the contrary, the adjusted geometric mean concentration of erythrocyte folate was higher among women with obesity rather than women with normal weight or overweight, suggesting that BMI may affect the body distribution of folate. Among both supplement users and non-users, the adjusted geometric mean erythrocyte folate concentrations were higher among women with obesity while, within each BMI category, the adjusted geometric mean concentration of erythrocyte folate was higher among supplement users than non-users.

Da Silva *et al.*[15] analysed the relationship between BMI and the short-term pharmacokinetic response to an oral dose of folic acid. Sixteen healthy women with obesity and sixteen women with normal weight of childbearing age (18–35 years) were administered a single oral dose of folic acid (400 µg). Blood samples were collected at baseline and after 10 h period. At baseline they found lower plasma folate ($P<0·005$) and higher erythrocyte folate ($P=0·05$) in the group with obesity; the authors do not report if a folate status deficiency occurs through the observed population; plasma folate reference interval and/or cut-off values were not reported. The AUC for the absorption phase (0–3 h), peak plasma folate concentrations and overall plasma folate response (0–10 h) were lower in women with obesity *v.* normal weight, suggesting that body distribution of folate is significantly affected by obesity.

Finally, De Luis *et al.*[26] analysed vitamin status (A, D, E, K, B_{12} and folate) as well as micronutrient status (Zn, Cu, phosphate, Ca) in a group of 115 women with a mean age of 43 years with morbid obesity, candidate to biliopancreatic diversion surgery; although no distinction between women of childbearing age and perimenopausal ones was reported, we included this study. The recruited population was divided into four groups ($35 \le BMI < 40$ kg/m^2; $40 \le BMI < 45$ kg/m^2; $45 \le BMI < 50$ kg/m^2; BMI ≥ 50 kg/m^2), with no differences in height and age. The results of this observational study highlighted that plasma folate levels were <3 ng/ml in 25·2 % of the sample; moreover no association between BMI and folate levels was found[26].

Discussion

Obesity and excess weight during pregnancy are associated with a number of complications during childbirth through the influence on the intra-uterine growth of the fetus. There is an increasing interest in nutritional status before and during pregnancy as well as in nutrient intake and their effects on offspring. Folate status in women with overweight/obesity may be altered and may be a possible contributor in increasing the risk of congenital birth defects, particularly NTD. A potential hypofolataemia in fertile women affected by overweight/obesity could be responsible for a higher risk of NTD in the offspring. However, only a few studies have shown an interest in analysing folate status in childbearing-age women with overweight/obesity, and these results are discordant.

In fact, some reported studies showed suboptimum levels of plasma folate in a high percentage of women with overweight (45 %)[19] and/or obesity (25·2 %)[26] while others describe no significant difference in folate levels between the groups of women with and without obesity[22,23].

https://doi.org/10.1017/S0954422417000142 Published online by Cambridge University Press

Additionally, with regards to the positive association between BMI and folate concentration, results are conflicting: some authors described a positive association between BMI and folate levels[19,26] while others did not[24,26]. Finally, only two studies evaluated plasma and erythrocyte folate concentration, a measurement that could be very important as more discussions ensue[15,25].

This heterogeneity of results could be due to several methodological aspects and other unassessed factors, such as level of education and socio-economic status[27], alcohol consumption or drug intake[28], which might influence plasma and erythrocyte folate levels and might help explain folate deficiency in women of childbearing age with overweight/obesity.

Folate deficiency definition

Objective data from the clinical laboratory are critical for medical decisions, including initial diagnosis and monitoring of treatment outcome. Laboratory errors, including inaccurate reference intervals or cut-off values, can lead to inappropriate diagnosis, unnecessary test repetitions and inappropriate follow-up investigations. Moreover, excessively wide reference intervals may mask subclinical disorders, and the use of incorrect reference intervals or cut-off values may confuse the clinical picture. Therefore, relevant reference intervals or cut-off values are required for a correct test result interpretation[29].

An initial fall in plasma folate concentration below 6·8 nmol/l (3 ng/ml) followed by a progressive depletion of folate stores trigger bone marrow to generate macrocytic cells with abnormal nuclear maturation[6]. Based on the microbiological *Lactobacillus casei* subsp. *rhamnosus* assay, cut-off values for plasma and erythrocyte folate deficiency have been set at 6·8 nmol/l (3 ng/ml) and 140 ng/ml (317 nmol/l), respectively[6].

Thakur *et al.*[30] reported that a subject is considered to be folate deficient if plasma and erythrocyte folate concentrations are less than 2 and 150 ng/ml (4·5 and 340·9 nmol/l), respectively.

Wartanowicz *et al.*[20] considered plasma folate levels ≥14·9 nmol/l as the optimum cut-off value, with plasma folate levels ≥13·6 nmol/l as the lower limit of the range of plasma folate concentration associated with very low risk for NTD. In woman with overweight and obesity who are planning to get pregnant, the use of this cut-off value might be more appropriate in order to minimise the risk of NTD. Additionally, experts[2,31,32] agree that erythrocyte folate levels above 1000 nmol/l are required for optimal NTD prevention.

The studies presented in this review reported different cut-off values: Hirsch *et al.*[18] used a cut-off value of >6·8 nmol/l; Ortega *et al.*[19] stratified the population by using the cut-off values of ≥14·9 and ≥13·6 nmol/l; Stern *et al.*[22] used a cut-off value of >15·9 nmol/l; De Luis *et al.*[26] used a cut-off value of >3 ng/ml; Ruiz-Tovar *et al.*[23], Baltaci *et al.*[24], Tinker *et al.*[25] and da Silva *et al.*[15] did not specify the cut-off values considered.

Since the different cut-off values used to define plasma and erythrocyte folate deficiency were not always reported in these studies, the diagnosis of folate status deficiency in women with obesity could lack uniformity.

Erythrocyte folate levels and supplementation

A single measurement of plasma/plasma folate provides little information on the folate status and body stores[33]. Erythrocyte folate content is known to reflect long-term average consumption and tissue stores since erythrocytes accumulate folate merely during erythropoiesis[33].

Recent studies conducted on folic acid fortification described a paradoxical phenomenon. Obesity exhibits low fasting plasma folate but high erythrocyte levels of folate[33]. Additionally, subjects with obesity reported higher levels of plasma folate oxidation products (5-methyltetrahydrofolate oxidation product; MeFox) than subjects without obesity because obesity is found to be associated with increased activity of cytochrome P450 (CYP) 2E1, a mono-oxygenase enzyme that can use folic acid as a substrate[33].

Tinker *et al.*[25] evaluated erythrocyte folate levels, suggesting that erythrocyte folate concentration was higher among women with obesity, particularly in the supplemented ones, while plasma folate concentration was significantly lower in those with obesity compared with those with overweight or normal weight. These findings were in agreement with previous results[33]. In fact, Zhou *et al.*[33] reported that dietary folate deficiency led to a lower plasma folate concentration, up-regulating trans-epithelial transport and enhancing cellular uptake of the developing erythrocyte.

Stern *et al.*[22] sought to find an explanation of why the folate status of women with obesity differs compared with those with normal weight or overweight, and they attributed it to the differences in metabolism; in fact the area under the time–concentration curve (AUC) was found to be significantly higher in those with obesity when defined as a function of total body weight, underlining that folate does not freely distribute into adipose tissue. When the AUC was defined as a function of dose per kg of LBW, it was found to be significantly higher in the group with obesity ($P = 0{\cdot}008$), with individuals with obesity having higher weight and body fat but also more LBW. The author concluded that peri-conceptional supplementation recommendations might need to be adjusted to account for LBW differences in the population with obesity, which provides initial evidence that LBW, which also increases as total body weight does in obesity, significantly affects folic acid pharmacokinetics. Nevertheless, increased storage in erythrocyte levels does not mean fetal safety from NTD since there could be amplified plasma 5-methyltetrahydrofolate oxidation products suggesting increased degradation of folate[33].

Genetic factors

Some polymorphisms of genes encoding enzymes and transport proteins involved in folate metabolism have an impact on folate status and health consequences; it has been suggested that the 677C→T polymorphism of the gene encoding the methyltetrahydrofolate reductase (MTHFR) enzyme has the highest impact on folate metabolism[6]. MTHFR converts 5,10-methylene-THF to 5-methyl-THF 785 providing one-carbon unit for the methylation cycle. Homozygosity for the T allele is associated with reduced enzyme activity (up to 70 % lower) and

https://doi.org/10.1017/S0954422417000142 Published online by Cambridge University Press

about 20–25 % lower plasma folate and higher plasma total homocysteine concentrations compared with the 677CC genotype[6]. Studies reported in the present review did not evaluate this aspect.

Lifestyle factors

Lifestyle factors such as dietary intake, cigarette smoking and alcohol intake affect folate status[30,34,35]. Micronutrient deficiencies (including folate) associated with overweight and obesity may result from increased intake of relatively cheap, energy-dense but nutrient-poor food[36], and folate levels might be influenced by metabolism alteration, which can occur in obesity[37]. The recommended intake is 400 μg/d[38,39] and Stern *et al.*[22] reported that women with a BMI indicative of obesity (≥ 30 kg/m^2) would need an additional 350 μg of folic acid per d to reach a folate status analogous to those with a lower BMI.

Excessive alcohol[30] and coffee[40] consumption can also lead to folate deficiency and, as concerns cigarette smoking, several mechanisms (such as decreased dietary intake, reduced absorption, diminished hepatic uptake, increased urinary excretion, possible interaction between chemical components of cigarette smoke and folate coenzymes) may explain folate deficiency in smokers[34,41].

Oral contraceptives

Recently Shere *et al.*[42] conducted a systematic review and meta-analysis on the effect of oral contraceptives on plasma and erythrocyte folate concentrations to ascertain how the reduction in blood folate concentrations is associated with oral contraceptive use. No studies presented in this review have considered oral contraceptive use.

Bariatric surgery and restrictive diet

Finally, weight loss induced by bariatric surgery is a major factor implicated in folate status in childbearing-age women affected by severe obesity. Bariatric surgery is increasingly performed and evidence demonstrates that weight-loss surgeries lead to greater benefits than traditional weight-loss therapies among subjects with severe obesity. However, some bariatric surgical procedures may induce malabsorption and frequently result in nutritional deficiencies, such as folate deficiency[43,44]. Nutrient deficiencies may also occur after restrictive surgical procedures, such as adjustable gastric banding, because of decreased food intake and dietary imbalances[44]. Furthermore, even unbalanced or very-low-energy diets may induce nutrient deficiencies[45] because of poor nutrition or dietary restriction that prevents meeting the requirements[46], leading to a decreased folate intake, which is particularly risky in the peri-conceptional period. On the other hand, hypoenergetic balanced diets may also maintain or even improve folate status either because they are rich in vegetables and fortified cereals, or because weight loss *per se* may modify the folate metabolism through a reduction in the erythrocytes' uptake[15,22].

Clinical practice

As described in this review, there are relatively few and discordant results regarding folate levels in women of childbearing age affected by overweight/obesity, and further studies need to be conducted in the greater population, taking into account the multiple variables that can affect folate metabolism. Nevertheless, it is important to assess the folate status in women of childbearing age with overweight/obesity who plan to become pregnant to prevent NTD.

Non-pregnant women with obesity, including those of childbearing age, have shown lower plasma folate and higher erythrocyte folate than normal-weight women. Since the placenta takes up folate from the maternal plasma and the placental uptake of circulating folate ensures an adequate folate supply to the developing fetus, low plasma folate in women with obesity could increase the risk for NTD-affected pregnancy even after adjustment for dietary and supplemental folate intake. Women of childbearing age with obesity may therefore require supplemental folic acid to increase or maintain a plasma folate status that is associated with maximal protection from NTD[47].

Folate status should be assessed both by plasma and erythrocyte levels and practitioners should take into account several other factors such as dietary intake (fruit and vegetable consumption and/or fortified foods and/or vitamin supplementation), lifestyle factors (cigarette smoking and alcohol consumption) and genetic factors, oral contraceptive use, and previous weight-loss programmes or bariatric surgery.

Although major health organisations promote the use of folic acid in women of reproductive age through clinical guidelines and recommendations, the EuroPrevall study[48] has revealed that maternal dietary habits as well as the use of dietary supplements during pregnancy vary significantly across Europe. The authors suppose that communication is scarce and has a low level of efficacy, which suggests that further investigation on dissemination of recommendations and on factors associated with long-term compliance might be useful for improving public health strategies to promote healthy pregnancies and pregnancy outcomes.

Additionally, the prevalence of folic acid supplementation is reported to be high in the prenatal period, while most women do not use folic acid in the peri-conceptional period, even if they are aware of the benefits[49]. Since it is estimated that approximately one-third of pregnancies worldwide are unplanned and many women may be unaware of their pregnancy for a few weeks after conception, folic acid supplementation should be recommended to all women of childbearing age, particularly to those affected by overweight/obesity.

Recently, Cawley *et al.*[2], in a review of European guidelines on peri-conceptional folic acid supplementation, reported that 400 μg folic acid pre-conceptional supplementation for at least 12 weeks is required to achieve optimal levels in erythrocytes to prevent NTD.

Some might disagree with the need for folic acid fortification or supplementation since some studies suggest adverse health outcomes; however, data are conflicting.

Studies connected asthma incidence in childhood with folic acid supplementation during pregnancy[50,51], but the purpose of this

https://doi.org/10.1017/S0954422417000142 Published online by Cambridge University Press

review was to alert the health care community about the need to screen women at risk of folate deficiency in the pre-conceptional period. Recently, systematic reviews and meta-analyses have demonstrated a beneficial or neutral effect in the aetiology of cancer while in 2009 the European Food Safety Authority (EFSA) Scientific Cooperation Working Group (ESCO WG) on 'analysis of risks and benefits of fortification of food with folic acid' concluded that there were currently insufficient data to allow a full quantitative risk assessment of folate status and cancer[46,52,53].

Conclusion

In conclusion, folate status in women with overweight/obesity may be altered and may be a possible contributor in increasing the risk of congenital birth defects, particularly NTD. However, only a few studies have shown an interest in analysing folate status in childbearing age women with overweight/obesity, and results are conflicting. This heterogeneity of results could be due to several methodological aspects and other unassessed factors. Therefore, further studies need to be conducted in a larger population, which take into account variables that can affect folate metabolism, such as dietary intake, lifestyle and genetic factors, oral contraceptives or other drug use, previous weight-loss programmes, or a history of bariatric surgery.

Nevertheless, although results are so heterogeneous, and further studies are mandatory, physicians should screen the folate status in women of childbearing age both assessing plasma and erythrocyte levels to start a personalised and more adequate supplementation before conception. Women with obesity, those with recent weight loss or who follow a low-energy diet, and those who have an unhealthy lifestyle are most at risk for folate deficiency and insufficiency.

Limitations

The studies considered in this review have some limitations that should be acknowledged. First, study populations were small in number and often had a wide age range. There are differences in race/ethnicity and country of origin which should be taken into consideration, since in some countries, especially in Europe, there is no mandatory fortification while the USA and South America are regulated by different fortification policies; therefore data are not always comparable.

Acknowledgements

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Each author participated actively in the work and gave a substantial contribution. Each author read and approved the final submitted manuscript. S. M. conducted the bibliographic research and wrote the manuscript; R. D. G. helped to conduct the bibliographic research and interpret the data; F. C. S. helped to write the manuscript and check the English language; H. C. supervised, reviewed and helped draft the manuscript.

There are no conflicts of interest.

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