REVISTA CHILENA DE PEDIATRÍA
Sociedad Chilena de Pediatría
www.scielo.cl

Rev Chil Pediatr. 2017;88(2):199-206
DOI: 10.4067/S0370-41062017000200001

CLINICAL OVERVIEW

Folate and Pregnancy, current concepts. It is required folic acid supplementation?

Folatos y Embarazo, conceptos actuales. ¿Es necesaria una suplementación con Ácido Fólico?

Erika Castaño[a,*], Raúl Piñuñuri[a,b,*], Sandra Hirsch[a], Ana María Ronco[a]

[a]Laboratorio de Nutrición y Regulación Metabólica, Instituto de Nutrición y Tecnología de los Alimentos, Universidad de Chile, Santiago, Chile
[b]Escuela de Nutrición y Dietética, Facultad de Salud, Universidad Bernardo O'Higgins, Santiago, Chile
*Estos autores contribuyeron igualmente en la elaboración del manuscrito.

Received: 3-11-2016; Accepted: 23-3-2017

Abstract

Folate intake during pregnancy is essential for an adequate fetal and placental development, as well as for the long-term health condition. Because folate deficiency may induce fetal pathologies, including neural tube disease (NTD), several countries have set up public policies to fortify foods with folic acid (FA). Chile started the fortification of wheat flour with FA in the year 2000, decreasing in 43% the prevalence of NTD. However, despite the high consumption of bread (the main fortified food with FA) by our population, a high number of pregnant women consume FA supplements, exceeding the maximal recommended FA intake. Additionally, if the diet is reduced in vitamin B12, the optimal ratio folates/vit B12 may be altered, inducing changes in the methylation of specific genes and other metabolic pathways, affecting fetal development and the long-term health of the neonates. We think that, after 16 years of the initiation of the fortification of wheat flour with FA, it is necessary to evaluate the possible side effects of an excess of FS intake in the pregnant population and their offspring. This article shows current concepts about mechanisms of folates and vit B12 at cellular level, and their possible consequences of an elevated FA maternal intake on the offspring.

Keywords:
Folates;
folic acid;
vitamin B12;
food fortification;
folic acid supplementation;
fetal development;
fetal programming

Introduction

The gestational period is key for adequate fetal development and for a healthy life[1,2]. Different genetic, environmental and endocrine factors can influence positively or negatively during this period. The nutritional status of the mother is undoubtedly one of the main environmental factors that influence pregnancy. This includes the selection of foods, the nutrients contained in them, their metabolism and the transport of

Correspondencia:
Ana María Ronco M
amronco@inta.uchile.cl

them to the fetus through the placenta. The nutritional deficiency of B vitamins, including folates and vitamin B12, has been related to some alterations during pregnancy, such as low birth weight, premature births and fetal malformations, among others[3,4]. Neural tube defects (NTDs) are one of the fetal malformations caused by the deficiency of maternal folate, which is supplied in the period before conception and during the first month of fetal development, during which the closure of the naural tube occurs[5].

We present current concepts about relationship/interaction between maternal levels of folates and vit B12 and their possible effects on offspring. The search for the information was made through the virtual libraries "Pubmed" and "Scielo", using the descriptors folate, folic acid, vitamin B12, pregnancy, high levels, offspring. Priority was given to meta-analysis, randomized controlled trials and longitudinal studies.

Folic acid fortification and pregnancy

During pregnancy, folate requirements increase from 400 to 600 µg/day to ensure fetal and placental growth due to its critical role in DNA synthesis and cell replication[6]. Folate deficiency during this period has been associated with a number of complications such as preeclampsia, miscarriage, stillbirth, low birth weight, prematurity[3,7] and neural tube malformations, including spina bifida and anencephaly[5].

Due to the essentiality of folates in pregnancy and to the high incidence of congenital malformations associated with their deficits[8], North and South American countries promoted policies for food fortification or supplementation with FA. In Chile, the Ministry of Health (MINSAL) authorities implemented as of January 2000 a mandatory fortification of wheat flour with an amount of FA equivalent to 2.0-2.4 mg/1000 g of product[9]. In one post-fortification study, one year after its implementation, the prevalence of NTD births decreased by 43% (17.1 to 9.7 per 10,000 live births)[10].

In 2010, MINSAL (by its acronyms to 'Ministry of Health' in spanish) evaluated the flour fortification program and found that the levels of FA in fortified wheat flour exceeded the recommendation established by the Food and Drug Administration (FDA, USA)[9]. According to this evaluation, it was found that the concentration of FA in the samples (n = 175) was within a range of 0.02-7 mg/kg of product. Only 23% of the samples presented a fortification range within the established values (2.0-2.4 mg/kg) and, on average, the concentration of FA in the samples evaluated was 2.5 mg/kg. For this reason, MINSAL decided to modify the range of FA to levels between 1.8-2.6 mg/kg, a decree that came into effect from March 2012[9]; However, what was done was to expand the range of doses of fortification.

According to the National Food Consumption Survey (ENCA in spanish, 2010)[11] an adult woman consumes between 73 and 184 grams of bread a day containing 70% wheat flour[10]. According to MINSAL, 1 kilogram of flour has an average of 2,500 µg of FA, therefore the consumption of that amount of bread contributes between 128 and 323 µg of FA per day, without considering the consumption of other foods fortified with this vitamin as pastas, bakery products, breakfast cereals, cookies, etc. It should also be considered that studies that determine nutrient intake through dietary surveys tend to specifically underestimate folate intake[12]. Additionally, in the study by Hertrampf et al (2003), folate concentrations in women of childbearing age increased significantly from FA fortification[13]. In studies where circulating folate concentrations have been determined in a general adult population, it was found that 12%[14] and 40%[13] had baseline levels reported as normal. Considering the high consumption of bread in Chile, it is highly unlikely that there is folate deficiency.

Supplementation with folic acid

Another strategy to reduce the incidence of NCDs proposed by developed countries, such as USA, is the intake of supplements of 400 µg/day of FA in women of childbearing age and during the first 3 months of pregnancy[15]. In Chile, the regulations determined by MINSAL through the "Perinatal Guide 2015" suggests to start supplementation of 1000 µg/d of FA during the pre-conceptional period, and only if there is a history of neural tube malformation, it is supplemented with 4000 to 5000 µg/day[16]. With this scenario, one might think that a pregnant woman who covered her nutritional requirements of folates would hardly have deficiency of this nutrient; However, there is no information on the nutritional status of these vitamins in pregnant women in Chile. On the other hand, the consumption of FA supplements between 1000 and 5000 µg is clearly exceeding the maximum tolerable level (UL, Upper Level) set for FA (1000 µg/day)[6]. Although the UL is a safe value because if this amount is consumed does not mean a health risk, to date there are no studies that determine the adverse effects of consumption of FA in quantities higher than UL in humans. At present, it is of great interest to study the possible side effects of fortification with FA. Castillo-Lancellotti et al. (2010) estimated that the consumption of FA from fortified foods in children (from 8 to 13 years) in the post-fortification period could be exceeding UL[17].

Transport of folate to the fetus

Folates are transferred from the mother to the fetus through the placenta via 3 specific transporters (RFC, FOLR1, PCFT/HCP1)[18] in addition to additional efflux transporters belonging to the ABC superfamily that are present in the human placenta[19]. In our laboratory, we have found that placental folate transport varies according to birth weight[20] and gestational age[21]. In addition, preterm newborns (32-36 weeks of gestation) had higher serum folate levels and lower vitamin B12 levels compared to serum concentrations in term newborns[21]. The same was observed in small term infants for gestational age (SGA) compared to adequate term gestational age (AGA) infants[20]. These results suggest that there is an interaction between folates and vit B12 that is related to gestational age and to birth weight.

Some researches have pointed out that a possible maternal imbalance in the folate/vit B12 ratio would be related to the risk of developing early metabolic alterations in their offspring, increasing the risk of a higher concentration of adiposity and insulin resistance[22-24].

Interaction between folates and vit B12 - Folate trapping

Folates participate in the metabolism of 1-carbon compounds and together with vit B12 contribute to the synthesis of methionine and S-adenosylmethionine (SAM), substrate of methylation reactions in the body. DNA methylation is one of the most studied epigenetic mechanisms in vertebrates[25]. During pregnancy, vit B12 requirements increase from 2.4 to 2.6 µg/day[6]. In Chile, the consumption of this vitamin in women aged between 14 and 64 years is 1.6 µg/d (95% CI 0.7 to 3.0 µg/d), being higher in rural areas[11]. Additionally, it has been observed that 10% of women in reproductive age have vit B12 levels below 149 pmol / L and 13% below 185 pmol/L (vit B12 deficiency or marginal status is defined in adults as values < 148 pmol and 148-221 pmol[26], respectively). In contrast, no folate deficiency was found in this population[13]. The highest risk of vit B12 deficiency would be in vegetarian women[27] because the major source of this vitamin is found in meat products. In Chile, only the prevalence of vit B12 deficiency in older adults is estimated to be in the range of 25.4 to 54.1%[28].

In conditions of adequate circulating levels of folates and vit B12, homocysteine (Hcy) is converted to methionine by the action of methionine synthase (MS) using 5-methyltetrahydrofolate (5-MTHF) as substrate and vit B12 as cofactor. This reaction generates SAM and tetrahydrofolate (THF); If homocysteine is not degraded in this pathway, it can enter the transsulfurization pathway where cysteine is generated and from it glutathione is synthesized[1,29] (Figure 1A). In addition, the available vit B12 acts mainly as a cofactor of two important enzymes, MS and methyl malonyl CoA mutase (MMCoAM), the latter catalyzes the conversion of methyl malonyl CoA (MMCoA) to succinyl CoA to enter the Krebs Cycle[30] (Figure 1A).

When plasma levels of folate (elevated) and vit B12 (deficiency) are altered, a mechanism known as a "folate trap" operates, in which folates are trapped as 5-MTHF, the main circulating form of folate in plasma And at the cellular level[31], and the methionine synthesis process is inefficient, resulting in Hcy accumulation and SAM decrease[3,25]. SAM is required for the methylation of DNA, proteins and lipids[32], consequently, under poor conditions of SAM an alteration occurs in these reactions. In addition, SAM acts as an allosteric activator of cystathionine-β-synthetase (CβS)[33], an enzyme that catalyzes the degradation of Hcy via transsulfurization to cystathionine, using vitamin B6 as a cofactor; It is subsequently converted to cysteine; Important precursor of glutathione[34]. Glutathione (γ-glutamyl-cysteinyl-glycine, GSH) is the main molecule involved in the equilibrium of the oxidation-reduction reactions in cells[35]. GSH concentrations decrease dramatically under conditions of oxidative stress or by a decrease in the availability of their precursors. Therefore, if the availability of SAM decreases, as a consequence of the folate trap, the CβS can not be activated and, consequently, the Hcy can not be re-methylated or degraded, releasing itself into the plasma where it is susceptible to oxidation, Increasing the reactive oxygen species and generating a decrease in glutathione availability[34] (Figure 1B).

Another consequence of the folate trap is that high folate levels must be rapidly metabolized for which concentrations of methylcobalamin (MeB12) should be sufficient to act as a cofactor for MS (Figure 1B). This condition would generate an increase in the oxidation of Vit B12, decreasing its flow towards the mitochondria[30], possibly generating an intracellular depletion of vit B12. Consequently, a high intake of FA could be leading to vit B12 deficiency. However, additional studies are required to test this hypothesis.

Folate trap in pregnancy and fetal genes program

According to the Barker hypothesis[36], adverse environmental effects during conception, fetal development and in early life condition are the onset of metabolic diseases in adulthood[37]; However, the mechanisms by which an event during gestation affects the phenotype at a given age have not been fully elu-

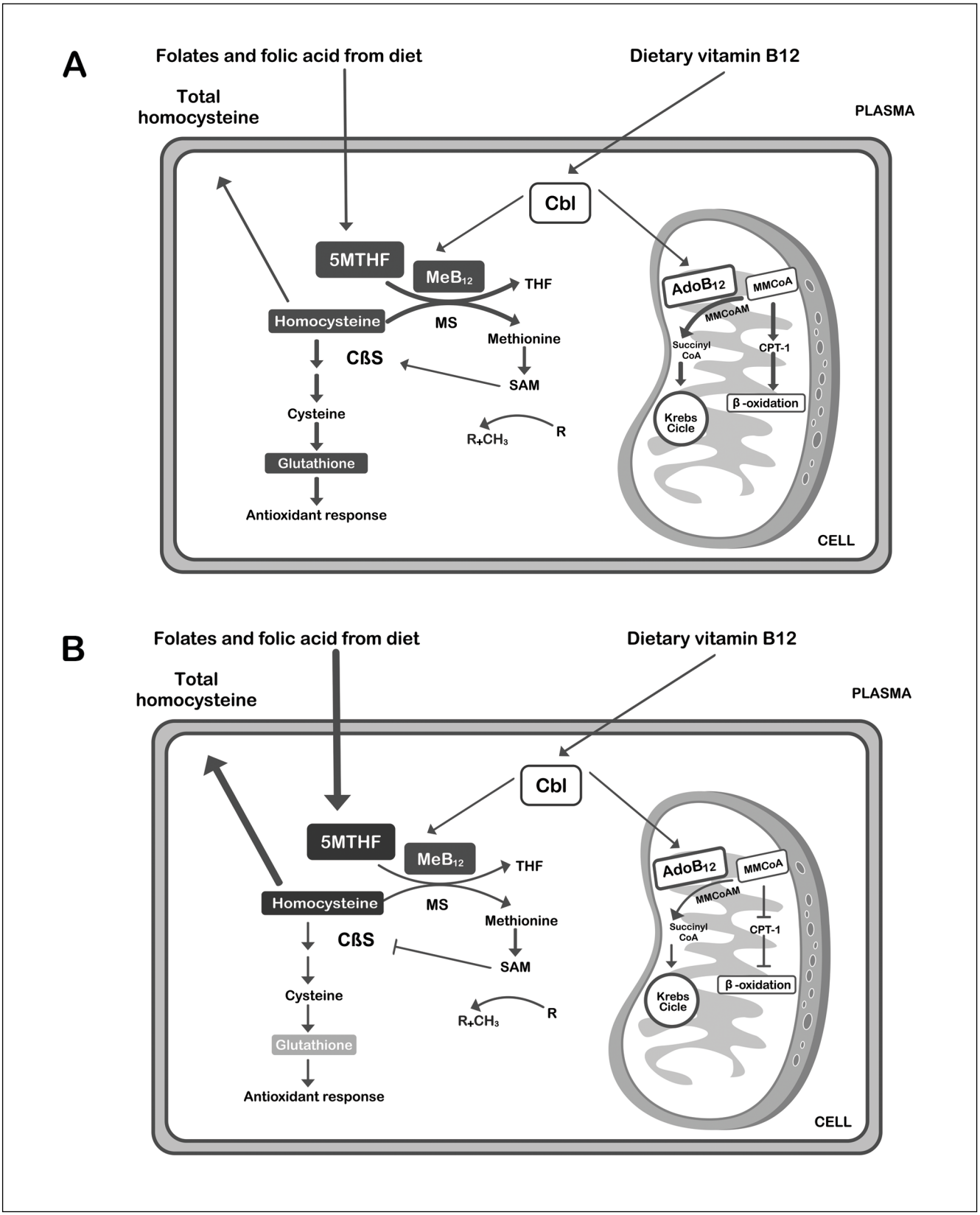

Figure 1. Folate and vit B12 metabolism. **A.** Metabolism under normal conditions. **B.** Metabolism under high folate/vit B12 conditions. Abbreviations: 5-MTHF, 5-Methyltetrahydrofolate; THF, Tetrahydrofolate; CβS, Cystathionine β-synthase; MS, Methionine Synthase; SAM, S-Adenosylmethionine; MeB12, Methyl Vitamin B12 or Methylcobalamin; AdoB12, Adenosyl Vitamin B12 or Adenosylcobalamin; MMCoAM, Methylmalonyl CoA Mutase; MMCoA, Methylmalonyl CoA; CPT-1, Carnitine Palmitoyltransferase 1.

cidated. Recent evidence suggests that under adverse environmental conditions epigenetic mechanisms may be altered[38].

Alterations in availability in methyl group donors (folate, vit B12, betaine, choline) would affect the expression of certain genes important for fetal development and long-term health of the individual[39,40]. Methylation reactions occur in CpG sequences located in regions of regulation of gene expression such that hyper methylation decreases gene expression and active hypomethylation[41].

In pregnant women supplemented with 400 µg/d FA, it was observed that methylation may be affected in a regulatory region of the insulin-like growth factor 2 (IGF2) gene, influencing intrauterine growth and consequently, birth weight[42]. In addition, a recent meta-analysis of approximately 2000 newborns found an association between maternal folate plasma levels and methylation of CpG sites in 320 genes[43]. These genes are related to different pathologies such as the adenomatosis gene polyposis coli 2 (APC2), involved in brain development and the etiology of cancer; The GRM8 gene, encoding a glutamate receptor, involved in neurodevelopmental disorders such as attention deficit hyperactivity and autistic spectrum; The SLC16A12 gene involved in juvenile cataract and renal glycosuria; The KLK4 gene involved in dental malformation; The ILHX1 gene involved in uterine developmental abnormalities; The IHH gene, involved in skeletal malformations, among others[43]. In summary, this paper[43] suggests that periconceptional folate concentrations are related to other birth defects not known so far.

In animal studies it was observed that high levels of FA during gestation affect the metabolic phenotype of offspring in adulthood, related to an increase in weight gain, glucose intolerance, increase in plasma insulin levels and decrease in adiponectin In females and leptin increases in males[44]. Maternal restriction of vit B12 has also been associated with increased body weight, fat percentage and lipid profile alterations in Wistar rats[45].

On the other hand, epidemiological studies have shown that alterations in the maternal levels of vit B12 present a higher risk of metabolic alterations in their offspring as: lower levels of HDL cholesterol[46], insulin resistance and greater adiposity[47]; Or alterations in maternal levels of folates, as evidenced in the PUNE-India study, that the folate concentration in red blood cells at 28 weeks of gestation was positively associated with adiposity and HOMA-IR index in their children at 6, 9.5 and 13 years of age[23,24].

The effects of maternal alterations of these vitamins on the development of insulin resistance (IR) obesity and cardiovascular disease (CVD) are not entirely clear. The alteration in vit B12 and folate levels and its relation with obesity, diabetes and insulin resistance could be explained by epigenetic modifications (hypo or hyper methylation) in certain genes. In addition, by alteration of lipid metabolism caused by Vit B12 deficiency because β-oxidation of fatty acids would be blocked by increased methyl malonic acid (AMM) which inhibits carnitine-palmitoyl transferase (CPT1) (Figure 1B) Leading to increased lipogenesis[22]. Another cause may be an increase in the oxidative stress given by the oxidation of Hcy in which super oxide and hydrogen peroxide are generated[34]. And by a decrease in GSH precursors such as cysteine[35].

During fetal development the contribution of folates and vit B12 is essential; Its deficiency has been associated with numerous alterations in the newborn, which has been reported in numerous scientific publications[1,3,17,48]. However, fortification of food and additional supplementation with FA during pregnancy, coupled with a low intakes of vit B12, could generate an imbalance in the folate/vit B12 ratio, whose long-term consequences are unknown. An increased ratio of folate/vit B12 during pregnancy alters DNA methylation, either by hyper or hypomethylation of specific genes, by inhibiting (protective genes) or by increasing (disease related genes) respectively, the expression of those genes permanently leading to long-term fetal genes program[43].

The current information allows us to argue that excessive FA intake, a condition that could be caused by the high consumption of food fortified with FA and additional supplementation, is not harmless. Therefore, in countries such as Chile, where FA-fortified food intake is high, FA supplementation during pregnancy, especially in the last trimester, should be analyzed. In addition, and as a more extreme measure, the policy of fortification of wheat flour with FA could be reviewed, especially considering that this measure involves the whole population. Recent studies have found a temporal association between fortification with FA and colon cancer in Chile and other countries[49].

Ideally, intensify the control of the fortification to avoid over-fortification. One of the alternatives used in European countries that do not have a fortification policy with FA is pre-conception supplementation and during gestation. Recently, Gildestad et al. (2016) have observed that the strategy mentioned has been associated with a reduction in the incidence of NCD in the period 2006 to 2013, presenting an adjusted relative risk of 0.54 (OR: 0.31-0, 91, 95% CI), that is, the consumption of pre-pregnancy FA supplements reduced the risk of NCD in the newborn by 46% similar to that observed in post-fortification of wheat flour with FA[50].

In summary, more human studies in this area would be required to contribute solid evidence to make the best decisions in the public policies of fortification and supplementation with FA.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

FONDECYT 1130188.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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