Academic Journal of
Pediatrics & Neonatology
ISSN 2474-7521

Juniper Publishers
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Mini Review
Volume 4 Issue 5 – June 2017
DOI: 10.19080/AJPN.2017.04.555705

Acad J Ped Neonatol

Folates during Pregnancy: Food Fortification versus Supplementation with Folic Acid

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Submission: March 07, 2017; **Published:** June 06, 2017

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Abstract

Folates are essential during pregnancy not only for cellular proliferation and purine synthesis but also to prevent neural tube defects (NTDs). As folates requirements increase during pregnancy from 400 to 600ug/day, several countries have implemented public policy of food fortification with folic acid (FA), the synthetic form of the vitamin, to avoid the consequences of its deficiency. However, only about half of their daily requirement is covered by foods naturally containing folates (e.g., leafy vegetables, fruits, avocado, dairy products, eggs, meat, etc) and/or by foods fortified with FA, being wheat flour the most commonly used (e.g., bread, bakery, etc). Currently, most pregnant women consume additional FA in supplements, increasing their level of consumption to more than 1000ug/day, a level considered as the upper limit for FA during pregnancy by the Office of Dietary Supplements at NIH.

In this mini review we address the potential risks of higher than recommended FA consumption during pregnancy, especially when maternal diets are low in vitamin B12. We also discuss recent evidence of epigenetic changes induced by imbalanced folates/B12 maternal diets, and highlight the need for a re-evaluation of FA supplementation in countries with high consumption of fortified foods.

Keywords: Folates; Pregnancy; Vitamin B12; Food fortification; Supplementation; Folic acid

Introduction

Food fortification and supplementation with folic acid

Folates requirements for adults and pregnant women are 400 and 600µg/day, respectively [1]. Folates deficiency during pregnancy has been related to a variety of serious adverse health effects such as preeclampsia, spontaneous abortion, still-life, low birth weight, prematurity [2,3] and neural tube malformations including spina bifida and anencephaly [4]. Due to the increased prevalence of neural tube defects (NTD) and other fetal malformations associated to folate deficiency [5], several countries including the USA, Canada, Australia and in most of Latin America, impelled mandatory public policies of food fortification with FA; however, other countries, mainly those of the European Community, chose FA supplementation instead of food fortification during gestation [6]. For example, since 2000 the Latin American country Chile implemented a mandatory public policy to fortify wheat flour with an equivalent concentration of 1.8 - 2.6 mg of FA per 1000 g of product, as recommended by the Food and Drug Administration (FDA) [7]. According to a study performed a year after such policy implementation, food fortification had a profound positive impact by reducing in 43% the prevalence of NTD at birth (from 17.1 to 9.7 per 1000 live births) [8].

The strategy of FA supplementation implies that women have to plan their pregnancies and consume oral FA supplements of 400ug/day starting 4 weeks before conception until week 12 of gestation [9]. In the case of Chile, current legislation encourage initiation of FA supplementation with 1000 ug/day during the preconceptional period [10] despite a considerable consumption of FA already present in fortified foods. In fact, a recent study conducted in our laboratory showed that in a cohort of more than 1000 women who are pregnant or have delivered a baby in the last few days, about 78% of them consumed FA supplements during pregnancy.

In a previous study, folate concentrations in women at reproductive age were considerably increased after initiation of food fortification with FA [11]. Due to appropriate policy implementation, FA fortified foods are now consumed by the

whole population and as a consequence, an increase of blood folate concentration in the general adult population was measured. In about 12% of them, FA levels were found to be higher than the reference values reported as normal [12], and the levels of FA in the erythrocytes of women who consumed more than 400µg/day were found to increase significantly between the pre- and post-fortification period (from 689±170 to 732±159nmol/L) [11]. As could be the case for most developing countries, the high levels of fortified bread consumption by Chileans make folate deficiency highly unlikely. Interestingly, however, it was observed that high levels of folate coexist with low levels or even deficiency of vitamin B12 in women at reproductive age. In that report about 10% of reproductive-age women registered serum vitamin B12 levels lower than 149pmol/L and 13% of them, below 185pmol/L (the vitamin B12 deficiency and marginal status for this vitamin is defined in adults as <148 and between 148-221pmol/L respectively) [11].

Folates and vitamin B12 and their effects during pregnancy

When plasmatic levels of folates are high and vitamin B12 levels are low in the long-term, the health risks to both mother and offspring may increase. From the mechanistic point of view, some evidence suggest that the availability of methyl donors (e.g., folates, vitamin B12, betain and choline) is critical for the expression of several genes involved in fetal growth and development, all of which may affect the health of progeny in the long-term [13]. Epigenetic mechanisms, like DNA or gene-specific methylation, are probably the most altered reactions observed by an imbalance of the folate/vitamin B12 ratio. Gene methylation occurs in specific CpG sequences mainly located at the gene promoter region or in DNA pair bases related to the regulation of gene expression. For example, an hypermethylated Thau gene is less transcribed; an hypomethylated one is more expressed [14]. Along these lines, there is evidence that the methylation in a specific regulatory zone of the IGF2 gene was altered in pregnant women supplemented with 400 ug FA/day. This treatment affected fetal intrauterine growth, and consequentially birth weight [15]. In a very recent report, Joubert et al. [16] performed DNA methylation analysis in 2000 neonates, and observed a positive association between maternal folate concentrations and methylation of CpG sites in 320 genes, some of which related to birth defects, neurological function and embrionary development. More recently, a survey study evaluated the consumption of foods containing methyl donors, and found that the intake of dietary methyl donors was associated with hypermethylation of the leptin gene (LEP), a hormone inhibiting food intake [17]. In addition, FA supplementation for more than 6 months previous to conception was associated with higher levels of methylation of the retinoid receptor (RXRA), which is involved in the sensibility to insulin, adipogenesis and fat metabolism [17]. RXRA hypermethylation has been related to an increase of the adipose tissue in offspring at 9 years old [18]. Concerning to the effects at metabolic and/or anthropometric levels, it has been observed in experimental animals,that maternal diets with FA and low vitamin B12 concentrations lead to offsprings with increased weight and fat gain, glucose intolerance, hyperinsulinemia, reduced adiponectin in females, increased leptin in males and alterations in the lipid profile [19,20].

Epidemiological studies have reported that maternal alteration on these vitamin levels lead to a higher risk of metabolic alterations in their offspring such as lower HDL cholesterol levels [21], insulin resistance and higher adiposity [22], and HOMA-IR at 6, 9.5 and 13 years of age [23,24]. On the other hand, we have observed that in preterm neonates (32-36 weeks) serum folate concentrations were higher and those of vitamin B12 lower than the levels measured in term neonates (37-41 weeks) [25]. Similar findings were observed in term neonates with a small birth weight compared to neonates with adequate birth weight [26]. Altogether, these results suggest that the interaction between folates and vitamin B12, likely by the methyl cycle, as well as an imbalance between them are related to gestational age and birth weight.

Discussion

We think that excessive FA intake, a situation that is easily reached when high consumption of FA fortified foods (mainly bread) is accompanied with FA supplementation, is not safe. For this reason, in countries with elevated consumption of fortified foods like Chile, additional FA supplementation should be carefully evaluated. A viable and effective alternative to food fortification is the strategy employed in European countries, where the standard recommendation is FA supplementation starting 4 weeks before conception until the end of the first trimester instead of FA fortification of some types of food. Along this line, a recent study reported that this strategy led to a reduction of 46% in the prevalence of NTDs between 2006 and 2013 [27]. Such reduction is comparable to that observed in Chile after a year of wheat flour fortification with FA. Finally, food fortification with FA affects the whole population and not only a specific segment of it, and could lead to unknown long-term consequences. A potential consequence relates to increased risk of methylation of tumor suppressor genes, observation recently made by our group (unpublished results).

Conclusion

Maternal diets with an imbalance between FA (high) and vitamin B12 (low) may induce adverse health effects not only on mothers and the developing fetus, but possibly, in the long time, increasing the risk of pathologies in the offspring. This hypothesis has not yet been demonstrated and requires long- term follow-up studies with animals and newborns.

Acknowledgement

We thank Fondo Nacional de Ciencia y Tecnología (Gobierno de Chile), FONDECYT #1130188 and CONICYT-PCHA/Magíster Nacional 2016-22150940.

How to cite this article: Raúl P, Erika C, Ana M R. Folates during Pregnancy: Food Fortification versus Supplementation with Folic Acid. Acad J Ped Neonatol. 2017; 4(5): 555705. DOI: 10.19080/AJPN.2017.04.555705.

Conflict of Interest

Authors declare that they do not have conflicts of interest.

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