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Review articles

The impact of folic acid supplementation on gestational and long term health: Critical temporal windows, benefits and risks

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ABSTRACT

Maternal folic acid (FA) supplementation is one of the most popular nutritional interventions during pregnancy for its protective effect against neural tube defects (NTDs).

The purposes of this review are: (a) to gather the current evidence regarding supplementation of maternal diet with FA and (b) to problematize the available literature in terms of dosages, critical temporal windows, and its potential benefits and risks.

The expression (pregnancy OR fetus OR offspring OR mother) AND ("folic acid" AND supplementation) was searched on PubMed database, filtering for articles published from 2005 to 2014. Publications referring to FA supplementation during the periconceptional period or pregnancy in which there was a conclusion about the effects of isolated FA supplementation on pregnant woman, pregnancy or offspring were included. Of the initial 1182 papers, 109 fulfilled the inclusion criteria.

The majority of the publications reported FA supplementation outcomes on offspring's health, with emphasis in NTDs, allergy/respiratory problems, cancer and behaviour problems. Some inconsistency is observed on the impact of FA supplementation on different outcomes, except for NTDs. It is also visible an increased concern about the impact of excessive supplementation, either in terms of doses or exposure's duration.

In conclusion, there is a growing interest in FA supplementation issues. The protective effect of FA supplementation over NTDs has been confirmed, being the periconceptional period a critical window, and it is frequently suggested that allergy/respiratory outcomes arise from (excessive) FA supplementation particularly later in pregnancy. Further research on critical doses and time of exposure should be conducted.

Introduction

Folate is a term that refers to a group of water-soluble vitamins of the complex B which are naturally found in foods such as leafy green vegetables, citrus fruits and liver. Folic acid (FA), the synthetic and completely oxidized form of folate, is used in vitamin supplements and in fortified cereal products.

Within the cells, folates act as cofactors in reactions which are determinant in cell division and cell maintenance, as well as in the regulation of gene expression through epigenetic mechanisms.[1] Indeed folates are a source of s-adenosylmethionine, the main cellular methyl donor that modulates genome-wide methylation thus regulating the expression of genes. This is believed to be the process by which folates affect foetal programming. In addition, folates have a determinant role in the re-methylation of plasma homocysteine to methionine,[2] for which blood folate levels correlate negatively with blood homocysteine levels.

Maternal FA supplementation is one of the most popular nutritional interventions during pregnancy and it has been extensively studied for its effect on neural tube formation and foetal growth[3] as folate deficiency at conception and during pregnancy may lead to abnormal development.[4]

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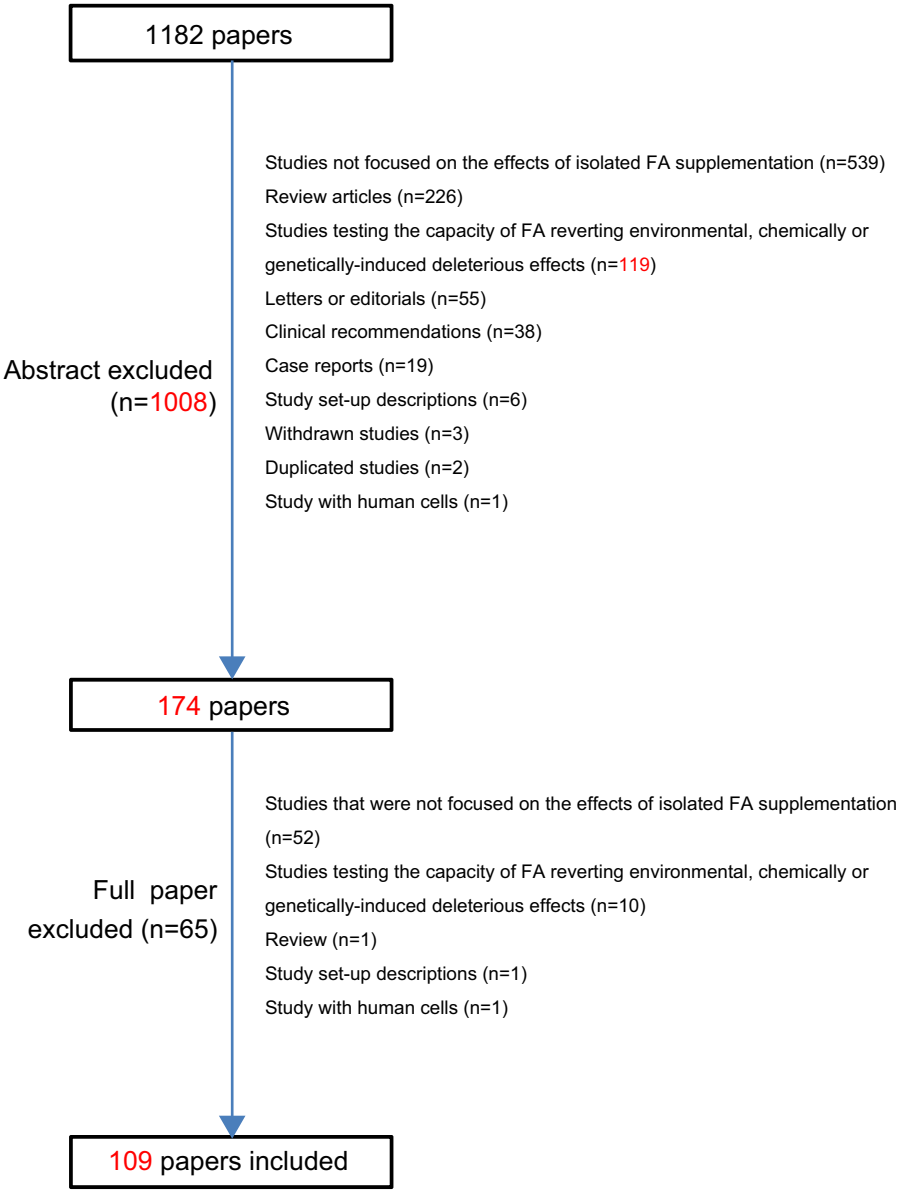

Fig. 1. Flow chart of process of systematic literature search.

Particularly since the 1990s, when evidence emerged about the protective effect of FA supplementation against the recurrence and occurrence of neural tube defects (NTDs),[5,6] there has been increasing concern about the role of periconceptional dietary supplementation and fortification strategies, as NTDs represents an important cause of morbidity and mortality.[7]

Many countries worldwide practice mandatory fortification of cereal grain products with FA, as a public health policy, and several EU countries maintain a voluntary fortification of different foodstuffs.[8] In addition, the WHO preconizes the supplementation with FA, in the periconceptional period and pregnancy, with 0.4 mg FA/day (together with 30–60 mg iron), increasing up to 5 mg/day for women at high risk of birth defects.[9] Notwithstanding, the WHO also pointed out that the protection against NTDs only happens when the supplementation occurs until the fourth gestational week, while supplementation in other time periods is likely to be beneficial in relation to other issues of maternal and foetal health, such as foetal growth and preterm birth. However, the evidence regarding these other outcomes is not consistent.

It is known that at 0.4 mg/day, all the oxidized form of FA is converted into biologically active metabolites during absorption, and so, its consumption is generally considered safe. Intakes above the recommended levels are likely to lead to the appearance of unmetabolized FA in foetal and maternal circulation, which has been demonstrated in countries with food fortification.[10] Although the impact of this is not completely understood, it is suggested that unmetabolized FA in maternal and foetal blood may act as methyl donor for the regulation of gene expression, with consequences in foetal programming.[11]

In Portugal, although the recommendations follow the WHO guidelines,[12] and there are multivitamin-mineral supplements containing 0.4 mg FA or similar (which are sold without a medical prescription), the available reimbursed pills containing isolated FA have a total dose of 5 mg. This dose corresponds to approximately 12.5 times the WHO recommended dose for low risk pregnancy. Furthermore, the lack of systematized health practices in many countries, being Portugal part of the problem, may lead to excessive FA supplementation resulting from the simultaneous use of FA pills and the consumption of FA-enriched foods or FA

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