CHAPTER 92

Excessive supplementation with folic acid during prenatal care: literature review

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ABSTRACT
Folic acid supplementation to prevent neural tube closure defects is recommended as part of prenatal care. The guidelines recommend administering 400µg daily of FA, and this dose cannot exceed 1000µg daily. However, it is not uncommon to encounter cases in which the intake of FA exceeds the recommended doses, which is a worrying reality since the effects resulting from the chronic use of high doses of this vitamin are not yet fully understood. A broad analysis of the literature pertinent to this theme from the last 10 years, was verified and 09 articles were selected. Some of the harms that may be associated with excess FA in prenatal care include increased risk of developing childhood asthma, as well as upper airway infections and wheezing; exacerbation of B12 deficiency; fetal growth impairment; influence on brain development (autism); allergic reactions (eczema); cancer promotion (breast tumor and colorectal adenoma); increased insulin resistance in children; and risk of gestational diabetes. This study warns about the importance of the adequacy of the SUS in providing FA tablets at the appropriate dose for pregnant women since the tablets offered by SUS are at a dose of 5mg, which is approximately 10 times higher than recommended.

Keywords: Folic acid, Dietary supplementation, Prenatal

1 INTRODUCTION

Folic acid (FA) plays an important role in nucleotide synthesis and DNA replication, and its deficiency primarily affects rapidly dividing tissues (ULRICH and POTTER, 2006). FA deficiency in fetuses is associated with a variety of disorders, including defects in neural tube formation, resulting in fatal anencephaly or spina bifida, with varying degrees of impairment (BURDGE and LILLYCROP, 2012) . In pregnant women, it can lead to anemia, since the demand for folic acid increases during pregnancy (BRASIL, 2013).

Folate is directly related to the prevention of neural tube defects, as well as the prevention of other diseases such as cardiovascular problems, Alzheimer's disease, some types of cancer, among others. Several studies have shown that this vitamin can help in decreasing plasma homocysteine concentrations, reducing acute myocardial infarction and cerebrovascular diseases. Folate deficiency can be caused by different conditions, such as a low folate diet or decreased absorption, for example, from alcoholism. Certain

conditions such as pregnancy or cancer result in increased rates of cell division and metabolism, implying an increase in the body's demand for folate. Some medications can also contribute to this deficiency, such as trimethoprim , methotrexate, anticonvulsants and birth control pills. A folate-deficient diet can lead to the development of megaloblastic anemia after four months, in addition to potassium deficiency (ALABURDA and SHUNDO, 2007) .

Supplementation with FA is a strategy for the prevention or treatment of developmental defects. Therefore, supplementation in pregnant women is related to the search for reducing the incidence of neural tube defect (NTD), which is the most common congenital malformation during pregnancy. The supplementation of PA during pregnancy was initially proposed in 1964, with this objective (BURDGE and LILLYCROP, 2012) .

Several countries have regulated PA supplementation 3 months before conception and during the first trimester of pregnancy with a dose of 400µg daily, which can be increased to 5mg daily if the woman has a previous history of having a child with this malformation (BURDGE and LILLYCROP, 2012) . Since the implementation of fortification, the number of NTDs has decreased significantly (MURRAY; SMITH and JADAVJI, 2018) .

According to the Brazilian Ministry of Health, folic acid supplementation to prevent neural tube malclosure is recommended as part of prenatal care and should be started in the preconception period, at least 30 days before the date on which it is planned to become pregnant, and maintained throughout pregnancy (BRASIL, 2013). In Brazil, until 2012, the daily use of 5mg of folic acid was recommended until the end of pregnancy. However, currently, the guidelines emphasize that 400 µg of folic acid daily should be administered to all women until the end of pregnancy, and this dose cannot exceed 1000 µg daily. (BRAZIL, 2013). However, it is not uncommon to come across cases where folic acid intake exceeds recommended doses. Therefore, both mother and fetus are exposed to excessive doses of folic acid, which is a worrying reality, since the effects resulting from the chronic use of high doses of this vitamin are still not fully understood (ULRICH and POTTER, 2006).

Higher doses of PA are recommended in some special situations, such as: women with diabetes (VALENTIN et al., 2018) , epilepsy (BJØRK et al. , 2018) and a history of NTD (ASADI-POOVA, 2015) . In these cases, it is recommended to take a daily dose of 5000µg of PA (NAVARRETE-MUÑOZ et al., 2015) . Obese women also need higher doses of PA supplement. Association guidelines in the UK, Australia and New Zealand advise a higher dose of PA for obese women, while in the US and Canada the guidelines do not make a recommendation on this matter. Interestingly, in the US, fortification of foods with folate is mandatory, while in the UK, Ireland and other European countries it is voluntary. The recommendation for obese women in Ireland is a dose of 5mg per day, which is available on prescription, although there is little evidence in the literature to justify this specific dose (O'MALLEY et al. , 2018) .

Epidemiological studies have shown that a significant number of women who supplemented with PA during pregnancy exceeded the tolerable limit recommended by the Brazilian Ministry of Health of 1,000µg/day (HOYO et al., 2011; WEST et al., 2012) .

The clinical significance of chronic or high intake of PA is not well established. Therefore, concern has arisen regarding the potential health effects, as in addition to fortified products, there is also widespread use of supplementation, including vitamins used in prenatal care, as well as energy drinks that are fortified with various vitamins. High intake of supplemented PA, along with food fortification, resulted in elevated red blood cell folate values among pregnant women and women of reproductive age (LAMERS et al., 2018) .

Results from several studies suggest that FA supplementation can induce aberrant patterns of DNA methylation, and mechanically play a role in carcinogenesis (ULRICH and POTTER, 2006; BARUA; KUIZON and JUNAID, 2014) . However, a meta-analysis performed with 50,000 individuals evaluated the effects of PA and demonstrated that PA supplementation does not substantially increase or decrease the incidence of cancer. (VOLLSET et al. , 2013) . Furthermore, supplementation with AF-containing prenatal multivitamins has been seen to be associated with a significant protective effect in pediatric cancers such as: leukemia, pediatric brain tumors, and neuroblastoma (SINGER et al. , 2016) .

Although controversial, over-supplementation is involved in certain chronic diseases and does not reduce cardiovascular disease (SAUER; MASON & CHOI, 2009) . Furthermore, acute folate intake also results in downregulation of folate transporters in the kidney, causing a dysregulation in the process of renal folate uptake (THAKUR et al. , 2014) . Several randomized and observational studies have suggested that maternal multivitamin intake with AF during pregnancy may modulate pregnancy-related outcomes (TIMMERMANS et.al. , 2009 ; CATOV et al., 2009 ; CATOV et al., 2011) including outcome in offspring development.

In order to evaluate publications related to folic acid supplementation during pregnancy and possible consequences associated with excess folic acid, a comprehensive review of the literature relevant to this topic was performed. Given that there is no benefit from an intake of PA above the recommended dose, the current dose of PA from supplements offered by the SUS should be reassessed.

2 METHODOLOGY

A systematic review study was performed based on the *preferred criteria. reporting items for systematic reviews and meta -analyses* (PRISM), in October 2020, using the following MeSH descriptors (https://decs.bvsalud.org/) associated: “folic acid” AND “dietary supplementation” AND “prenatal”. Research from meta-analyses, systematic reviews, original studies and clinical guidelines were selected. The searches were performed by the VHL (http://brasil.bvs.br/) in the MEDLINE (https://medlineplus.gov/) and LILACS (https://lilacs.bvsalud.org/) databases , in publications of the last 10 years, in Portuguese and English.

2.1 INCLUSION AND EXCLUSION CRITERIA

Studies of pregnant or preconception women and children whose maternal supplementation with folic acid during pregnancy was known were included. The intervention evaluated was the effects of excessive folic acid supplementation during pregnancy.

Studies with animal models, duplicate articles, incomplete texts, and those not available in full *online*, as well as opinion articles and articles that deviated from the proposed theme were excluded .

2.2 DATA EXTRACTION AND RISK OF BIAS

The following data were extracted from each study: authors and year; study design; sample size; objective; effects of excess folic acid. The title and abstract of each search result were screened by two reviewers who independently applied the same inclusion and exclusion criteria. There was no dissent.

3 RESULTS

A total of 520 articles were found in the VHL (03/10/2020) when the descriptors “folic acid” AND “dietary supplementation” AND “prenatal” were used in association. After inserting the following filters: articles from MEDLINE and LILACS, in Portuguese and English, full articles and articles from the last 10 years, as well as the main subjects: folic acid, prenatal care and nutritional supplements, a total of 258 articles were selected. for reading titles and abstracts.

After reading the title and abstracts, 221 articles that did not describe excess folic acid were excluded. And later another 14 articles were excluded because they were studies with animal models. A total of 23 references were selected for full-text evaluation, with 9 articles being selected that described the consequences of excessive PA during pregnancy.

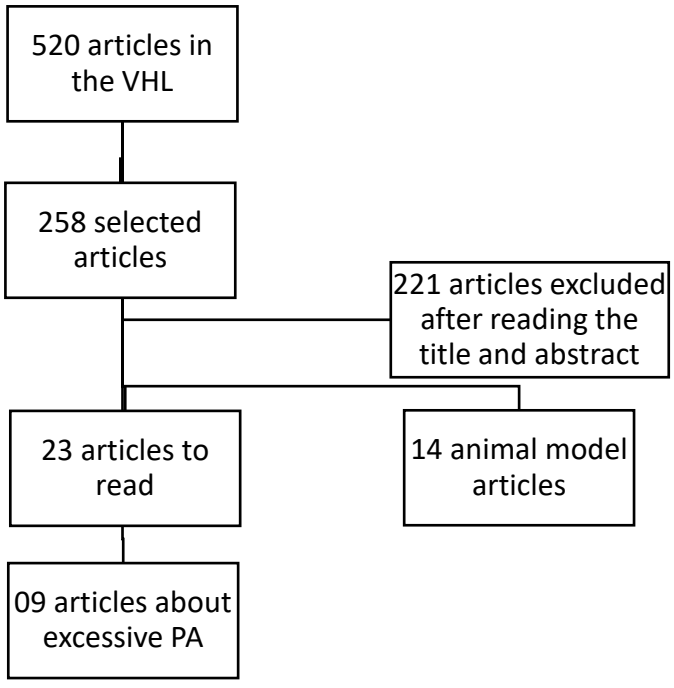
The flowchart for the search strategy is shown in Figure 1, and the selected articles are shown in Table 1.

Table 1. Articles selected in the review.

REFERENCE	STUDY	OBJECTIVE	EFFECTS OF EXCESS FOLIC ACID
DUNSTAN et. al., 2012	Prospective 628 pregnant women and 484 children	The relationship between maternal folate “ *status* ” during pregnancy, cord blood folate levels, and early childhood allergy problems	Higher doses of AF > 500µg/day given during the third trimester of pregnancy were associated with a risk of eczema and had no effect on other allergic conditions.
BARUA; KUIZON and JUNAID , 2014	Literature review	PA supplementation in pregnancy and health implications	• Dysregulation of renal folate uptake, • Asthma, • Influence on brain development, • Aberrant patterns of DNA methylation.
ASADI-POOYA, 2015	Literature review	To assess the safety of high-dose PA supplementation in women with epilepsy	Adverse effects on fetal brain development.

VALERA-GRAN et. al., 2017	Prospective 1,682 mother-child pairs	Effect of high maternal doses of PA supplements on neurocognitive development in 4- to 5-year-old children	The use of PA dosages exceeding 1000 µg/d during the preconception period was associated with lower levels of neurocognitive development
PARR et. al., 2017	Cohort 1,901 children and 1,624 mothers	Assess maternal folate intake during pregnancy and asthma in children	Pregnant women with FA at or above recommended supplementation, combined with a diet rich in folate, are associated with an increased risk of asthma in children.
LAMERS et. al., 2018	Workshop 38 health groups	Aligning recommendations for PA supplementation in pregnant women and women of childbearing age	• impairment of fetal growth, • cancer promotion, • Interaction with B12 deficiency, • Increased risk of asthma and autism.
MURRAY; SMITH and JADAVJI , 2018	Literature review	To determine whether excess maternal supplementation with FA affects child neurodevelopment	• Autism, • Late pubertal stage (13.5 years), • Increased insulin resistance (9.5 years and 13.5 years).
VALENTINE et. al., 2018	Literature review	AF supplementation in pregnancy	• Colorectal adenoma and breast cancer is cause for concern in older pregnant women, • B12 deficiency exacerbation, • Increased risk of respiratory infection and asthma in children.
HUANG et. al., 2019	Prospective 348 pregnant women at 16-18 weeks of gestation	To assess the association between duration of PA intake and risk of gestational diabetes mellitus in Chinese women.	Change in lipid profile in the second trimester of pregnancy and risk of gestational diabetes associated with prolonged use.

Figure 1. Evaluation flowchart of the articles obtained.



4 DISCUSSION

Several studies agree with regard to the ideal dose of folic acid that should be used in supplementation during pregnancy (ULRICH and POTTER, 2006; HOYO et al., 2011; BURDGE and LILLYCROP, 2012) . The WHO and the Ministry of Health (BRASIL, 2013) recommend a daily dose of 400 micrograms in order to avoid complications such as neural tube malformation, low birth weight and anemia during pregnancy. However, the Ministry of Health recommends different doses: 400µg/day for pregnant women, 1000µg/day in special situations during pregnancy – multiple pregnancy and 5mg/day for epileptic pregnant women (BRASIL, 2013).

The large number of pregnant women using high doses of PA may be related to medical reasons, as women with diabetes, epilepsy or a history of NTDs before pregnancy are recommended to take doses of 5mg/day (NAVARRETE-MUÑOZ et al., 2015). ; BJØRK et al. , 2018) there are also reports of increased doses of PA as prevention of oral clefts (WEHBY et al., 2012) . The use of these high doses of PA are unnecessarily continued after the third month of pregnancy (NAVARRETE-MUÑOZ et al., 2015) .

The guidelines of some countries, such as Ireland, advise a higher dose of PA for obese women (5mg/day), although there is no evidence in the literature to justify this dose. It has been observed in studies that obese pregnant women have a lower level of maternal folic acid and vitamin B12 than women with a normal BMI (O'MALLEY et al. , 2018; WEN et al., 2018) . The authors also guide vitamin B12 supplementation in obese women to prevent NCDs.

To determine the effectiveness of high-dose folic acid for preventing preeclampsia in women with at least one pre-existing risk factor: hypertension, gestational diabetes (type 1 or 2), or a body mass index ≥35, a a double-blind, multicenter, randomized controlled trial in 2464 pregnant women between 2011 and 2015 (1144 for the folic acid group and 1157 for the placebo group). Women were randomly assigned to receive either high-dose daily folic acid (four 1.0 mg oral tablets) or placebo between eight weeks and 16 weeks' gestation until the end of pregnancy. Folic acid supplementation at 4.0 mg/day in the first trimester did not prevent preeclampsia in women at high risk for this condition (WEN et al., 2018) .

A study among pregnant women in Spain showed that the majority of women did not follow the recommendations of 400µg/day of PA during pregnancy, using doses below or above the recommendation. More than half of the women used low doses of PA in the first and second period of pregnancy, due to previous pregnancy, smoking, alcohol consumption, unplanned pregnancy and no history of miscarriage. While 29% and 17% took high doses of PA, in the first and second period of pregnancy respectively, due to alcohol consumption, unplanned pregnancy and history of miscarriage. Public health strategies should be designed to raise awareness of the appropriate perception of PA use and to encourage healthcare professionals to avoid using PA dosages above or below current recommendations. (NAVARRETE-MUÑOZ et al., 2015) .

The considerable number of women who do not use PA can be explained in part by the fact that they were not aware of being pregnant and therefore were not informed of the benefits of PA in early

pregnancy. However, when women are aware of pregnancy and the benefits of PA, they increase PA use, particularly in the second and third month of pregnancy (NAVARRETE-MUÑOZ et al., 2015) .

AF is already added to foods for fortification in addition to the naturally occurring folate in foods. Thus, if FA supplements are also taken during pregnancy, the mother and fetus may be exposed to FA in excess of the recommended upper tolerable limit of 1,000µg/day for adult pregnant women. In the SUS, the dose of PA provided to the population of pregnant women is one tablet containing 5mg. This dose is above the dose recommended by the Ministry of Health of 400µg/day. Which exceeds the tolerable upper limit by 5 times. Thus, given the possibility of harm and the lack of proof of its efficiency when used in high doses, it is necessary to review the indication of excessive doses, especially those above 1,000µg/day.

For a better understanding of the effect of PA supplementation on pregnant women, we systematically reviewed the recent literature (2010-2020) in order to assess the health outcome of newborns and pregnant women. The limited number of studies included in this review, as well as the heterogeneity of their methodologies (Table 2), are the main limitations of this work. The literature review was difficult due to the inconsistent application of the term supplementation, which does not indicate high doses of PA consumption, and the application of the term “high”, which has different interpretations.

Table 2 . Methodology used by the 09 selected studies.

KIND OF STUDY	THE AMOUNT
PROSPECTIVE	3
WORKSHOP	1
LITERATURE REVIEW	4
COHORT	1

Of the 23 pre-selected studies, only 09 were included in the review, as they met the inclusion criteria, the other 14 studies did not report the effects of excess folic acid, therefore they were not included at the end of the review.

Of the 09 selected studies, 03 studies (DUNSTAN et al., 2012, VALERA-GRAN et al., 2017; HUANG et al., 2019) are prospective studies and 01 study (PARR et al., 2017) is a cohort study; these study models present better levels of scientific evidence. Four studies were selected (BARUA; KUIZON and JUNAID, 2014; ASADI-POOVA, 2015; MURRAY; SMITH and JADAVJI, 2018; VALENTIN et al., 2018) of literature review and 01 Workshop (LAMERS et al., 2018) between countries.

Two studies were excluded (HOYO et al., 2011; NAVARRETE-MUÑOZ et al., 2015) , as they only describe which population ingests high doses of PA. Two randomized controlled trials (WEHBY et al., 2012; BORTOLUS et al., 2014) were excluded. These studies have a strong power of experimentation, but they are not yet finalized. Most studies (SAUER; MASON and CHOI, 2009; PAPADOPOULOU et al., 2013; CZEIZEL; VERECZKEY and SZABÓ, 2015; SINGER et al. , 2016; SCHMIDT et al., 2017; ALFONSO et al., 2018; GOODRICH et al., 2018) describe only the benefits of PA intake. Two other studies recommend high doses (HUHTA and LINASK, 2015; BJØRK et al. , 2018) , for preventing heart

problems, and two other studies (O'MALLEY et al. , 2018; WEN et al., 2018) demonstrate that higher doses for obese women do not show great results.

4.1 EFFECTS OF EXCESS FOLIC ACID

Regarding the abusive use of folic acid, there is great uncertainty among the authors about the potential harmful effects that this vitamin could have on the health of the mother and the fetus when in excess. Some of the harm that may be associated with this excess are an increased risk of developing childhood asthma (PARR et al., 2017; LAMERS et al., 2018; VALENTIN et al., 2018) and the risk of upper airway infections and wheezing (PARR et al., 2017) in early childhood. In addition, studies indicate that excess folic acid promotes dysregulation of the process of renal folate uptake (BARUA; KUIZON and JUNAID, 2014) .

The high concentration of folate after fortifications may be influencing other normal biological processes, such as: aberrant patterns of DNA methylation (BARUA; KUIZON and JUNAID, 2014) and masking maternal vitamin B12 deficiency. Vitamin B12 deficiency is associated with impaired fetal growth (LAMERS et al., 2018) and irreversible neurological damage if not correctly diagnosed and treated (ASADI-POOVA, 2015; VALERA-GRAN et al., 2017) .

Excessive PA during preconception has also been associated with behavioral problems in children (VALERA-GRAN et al., 2017) . The study by Valera-Gran et al., 2017, suggests that the ingestion of high doses of PA can cause neurocognitive problems ; and corroborating with other studies, it can cause autism (LAMERS et al., 2018; MURRAY; SMITH and JADAVJI, 2018) .

Other theoretical risks are allergic reactions and eczema (DUNSTAN et al., 2012) as well as carcinogenic effects, since PA supplementation can increase the speed of proliferation of pre -neoplastic cells and subclinical cancers in pregnant women (BARUA; KUIZON and JUNAID, 2014; VALENTIN et al., 2018) .

More recent studies demonstrate changes in the pubertal stage in children aged 13.5 years; increased insulin resistance at 9.5 years and 13.5 years (MURRAY; SMITH and JADAVJI, 2018) ; change in lipid profile in the second trimester and risk of gestational diabetes (HUANG et al., 2019) .

The main effects of excess folic acid after reviewing the literature are described in table 3.

Table 3. Main effects of excess folic acid.

Too much folic acid	**Upper airway infections and wheezing (Asthma)**
	Dysregulation of the process of renal folate uptake
	Aberrant DNA methylation patterns
	B12 deficiency exacerbation
	Compromised fetal growth
	Late pubertal stage (13.5 years)
	Influence on brain development (Autism)
	Allergic reactions (Eczema)
	Cancer promotion (Breast Tumor and Colorectal Adenoma)
	Increased insulin resistance

	Change in lipid profile
	risk of gestational diabetes

Since folate levels can influence DNA methylation, further studies are needed in the future to explore the systemic differences in DNA methylation profile in relation to time and dosage of FA supplementation between different populations and between genders (BARUA; KUIZON and JUNAID, 2014) .

Huang et al., 2019 showed that most women take PA for a longer period, instead of following the recommendations of taking 400µg/day of PA for 3 months before pregnancy until the end of the first trimester. It was observed that duration or different periods of FA supplementation are associated with a higher risk of gestational diabetes when FA was taken for more than 90 days. It was also observed in this study that non-supplementation with PA during the prenatal period is related to the incidence of gestational diabetes. Thus, not taking AF or taking AF for a longer duration may not be safe for pregnant women (HUANG et al., 2019) .

The high intake of PA is related to Caucasian race, advanced maternal age and complete higher education (HOYO et al., 2011) , as they represent greater resources for access to PA supplementation, suggesting the need for reeducation in the entire population about the use of AF currently recommended.

Concern about the appropriate dose and potential side effects is still a matter of debate. As maternal FA supplementation has the potential to induce epigenetic effects in the offspring genome, which may vary with the individual's metabolic capacity, race, sex, geographic location or interactions with other nutrients, a possible reason for inconsistency between studies could be due to differences in the study design. In the future, there is definitely a global need for collaboration to accumulate scientific evidence from a clinical perspective, and to interpret these interventions and potential effects (BARUA; KUIZON and JUNAID, 2014) .

4.2 CLINICAL CONSIDERATIONS

Folate deficiency, a treatable condition, remains a public health concern. It should be known to everyone that 400µg/day of PA initiated 4 weeks before and up to 12 weeks after conception is effective. The exception is made for women with diabetes, epilepsy and a history of defects in the formation of the neural tube, who are recommended to take a daily dose of 5mg .

The PA pills offered by the SUS characterize an overdose. That is, the recommended dose is 400µg/day, and the currently offered dose of 5mg/day is approximately 10 times higher than recommended. Therefore, the adequacy of the SUS in providing pills in adequate doses is important.

5 CONCLUSION

The data presented in this review show that women of childbearing age should use with caution and not exceed the Ministry of Health's recommended daily intake of folic acid, as there is considerable

evidence that excess folic acid can lead to potential adverse effects for both mother and for the fetus. The dangers of high levels of folic acid, whether obtained through supplementation or naturally, are still not well understood. Therefore, additional studies are needed to determine the most effective dose of folic acid, the upper limit of folic acid intake, and the timing of folic acid supplementation.

Public health strategies should be devised to raise awareness of folic acid use in pregnancy and encourage healthcare professionals to avoid using folic acid dosages above current recommendations.

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