FOLIC ACID SUPPLEMENTATION AND REPRODUCTIVE HEALTH, TRANSCENDING THE PREVENTION OF NEURAL TUBE DEFECTS

SUPLEMENTAÇÃO DE ÁCIDO FÓLICO E SAÚDE REPRODUTIVA, TRANSCENDENDO A PREVENÇÃO DOS DEFEITOS DO TUBO NEURAL

SUPLEMENTACIÓN DE ÁCIDO FÓLICO Y SALUD REPRODUCTIVA, TRANSCENDIENDO LA PREVENCIÓN DE LOS DEFECTOS DEL TUBO NEURAL.

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ABSTRACT

Introduction: Folic acid is a vitamin that is traditionally prescribed to pregnant women in order to reduce the risk of neural tube abnormalities in the embryo, however, this practice should be reevaluated under the observation that many of the pregnancies are detected after the neural tube has formed and what would be the advantages or disadvantages after 28 days of gestation.

Development: Scientific evidence supports that folic acid supplementation is relevant from gametogenesis to the day of delivery, because it contributes to sperm meiosis, oocyte maturation, embryonic tissue formation and the growth of fetal organs and structures. At present, studies on folic acid toxicity do not show conclusive results and further research is needed to elucidate this issue.

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Conclusion: Adequate folic acid supplementation is important for reproductive health, directly influencing the proper development of gametes, the embryo/fetus, and the health of the pregnant woman.

Keywords: Folic Acid. Reproductive Health. Pregnancy (DESC/MESH).

RESUMO

Introdução: O ácido fólico é uma vitamina tradicionalmente prescrita a gestantes com o objetivo de reduzir o risco de anomalias do tubo neural no embrião; no entanto, essa prática deve ser reavaliada diante da observação de que muitas gestações são detectadas após a formação do tubo neural, levantando questionamentos sobre as vantagens ou desvantagens após 28 dias de gestação.

Desenvolvimento: Evidências científicas sustentam que a suplementação de ácido fólico é relevante desde a gametogênese até o momento do parto, pois contribui para a meiose dos espermatozoides, a maturação dos oócitos, a formação dos tecidos embrionários e o crescimento dos órgãos e estruturas fetais. Atualmente, os estudos sobre a toxicidade do ácido fólico não apresentam resultados conclusivos, sendo necessárias mais pesquisas para elucidar essa questão.

Conclusão: A suplementação adequada de ácido fólico é importante para a saúde reprodutiva, influenciando diretamente o desenvolvimento adequado dos gametas, do embrião/feto e a saúde da gestante.

Palavras-chave: Ácido Fólico. Saúde Reprodutiva. Gravidez (DESC/MESH).

RESUMEN

Introducción: El ácido fólico es una vitamina tradicionalmente prescrita a mujeres embarazadas con el fin de reducir el riesgo de anomalías del tubo neural en el embrión; sin embargo, esta práctica debe ser reevaluada considerando que muchos embarazos se detectan después de la formación del tubo neural, lo que plantea interrogantes sobre las ventajas o desventajas después de los 28 días de gestación.

Desarrollo: La evidencia científica respalda que la suplementación con ácido fólico es relevante desde la gametogénesis hasta el momento del parto, ya que contribuye a la meiosis de los espermatozoides, la maduración de los ovocitos, la formación de tejidos embrionarios y el crecimiento de los órganos y estructuras fetales. En la actualidad, los estudios sobre la toxicidad del ácido fólico no presentan resultados concluyentes, por lo que se requieren más investigaciones para esclarecer esta cuestión.

Conclusión: La suplementación adecuada de ácido fólico es importante para la salud reproductiva, influyendo directamente en el desarrollo adecuado de los gametos, del embrión/feto y en la salud de la mujer embarazada.

Palabras clave: Ácido Fólico. Salud Reproductiva. Embarazo (DESC/MESH).

1 INTRODUCTION

Studies on folic acid supplementation during pregnancy began with experiments by hematologist Lucy Wills, who studied the effect of the eating habits of pregnant women and megaloblastic anemia in the 1970s. The researcher observed that the anemia suffered by a group of Indian women had different patterns than the pernicious one, because supplementation with isolated vitamin B12 did not improve the clinical picture. However, with the consumption of a food product called marmite, the disease was prevented or cured. The possible nutrient of marmite was called "Wills' substance" and later, the compound was isolated calling it "folic acid", from then on studies were carried out that investigated the importance of folate during the gestation period (1,2).

Folic acid (pteroyl glutamate) is a vitamin whose active form is tetrahydrofolate and is conceived in health and nutritional sciences as the synthetic form of folates commonly found in foods such as legumes, green or dark leaves and citrus fruits (3). The most common chemical forms in which folate occurs in food groups are dihydrofolate (DHF), tetrahydrofolate (THF), folate mono and polyglutamates (4). On the other hand, folic acid is its synthetic form, it is more stable to oxidative degradation, this stability gives it the ability to have a high level of bioavailability and is found in fortified foods such as flours, pasta and bread (5). The intention of separating the concepts of folic acid and folate is that the bioavailability of folic acid is approximately 100%, while that of folate is 50%. The chemical structure of a folate is made up of a ring of pteridine that binds to a p-aminobenzoic acid Through a methyl group, P-aminobenzoic acid, in turn, binds to one or more glutamate residues by amide bonds (6).

The enterocytes of the jejunum and the ileum are the cells responsible for the absorption of folate at the intestinal level, and it is in these cells that the folate polyglutamates are hydrolyzed into folate monoglutamates, by the action of the catalytic enzymes polyglutamylcarboxypeptidase, produced by the pancreatic acini and Gammaglutamyl Hydrolase, whose action is dependent on the presence of zinc and is found in the apical pole of the enterocytes (7). Enterocytes have the following folate transporters in the microvilli: the reduced folate transporter that works with neutral pH, the proton-coupled folate transporter that works with acidic pH, and folate receptor proteins, FRα and FRβ, which are responsible for active transport since folate is a water-soluble vitamin that cannot cross the plasma membrane by itself. Additionally, it should be mentioned that this system is saturable, so folic acid supplementation should be in microdoses and preferably on an empty stomach (8,9).

After folate is absorbed by enterocytes, it is reduced by the action of dihydrofolate reductase (DHFR), to tetrahydrofolate (THF), this in turn is reduced and methylated

transforming into 5-methyl-tetrahydrofolate and is carried into the bloodstream through the capillary bed with the help of chaperone proteins such as albumin and folate transporter protein (10). 5-methyl-tetrahydrofolate (5-MTHF) is an excellent carbon donor and scavenger, so it is involved in several biochemical pathways within the cell, including methionine recovery, purine and deoxythymidine monophosphate (dTMP) synthesis, histidine catabolism, and serine-glycine interconversion (11).

In cells, 5-MTHF donates methyl groups for homocysteine methylation to generate methionine, so a low bioavailability of folic acid can result in homocysteine accumulation and impaired methionine synthesis. Following the process, methionine adenosyl transferase (MAT) transforms methionine into S-adenosylmethionine (SAM), responsible for donating methyl groups useful for DNA methylation and therefore the control of gene expression. SAM is also involved in the methylation of phospholipids, proteins, and neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, adrenaline, and nitric oxide) (12). On the other hand, the biochemical use of folate involves the participation of the enzyme methyltetrahydrofolate-reductase (MTHFR) and the production of the intermediate metabolite 5,10-methylenetetrahydrofolate, useful for the synthesis of thymidylate synthase (dTMP) during DNA replication and repair (13).

Taking into account the above, folic acid is described as a cytoprotectant and genoprotectant that promotes correct synthesis, stability and repair of DNA, so if there is a deficiency of this, epigenetic processes will be affected, especially those related to the de novo synthesis of DNA, the homocysteine-methionine process and the conversion of uracil to thymine. the latter can become considerably mutagenic if uracil (14).

Currently, folic acid supplementation during pregnancy has been carried out mainly due to the conviction that folate is necessary to prevent abnormalities related to failure in the closure of the neural tube (15). However, we must make the following reflection: after gastrulation, a portion of the ectoderm that forms the neural plate is consolidated in the cephalic segment of the neural tube by stimulation of the notochord and by the release of thee shh (Sonic the Hedgehog) (16). This activating molecule acts on the midline of the embryo by inhibiting the expression of Pax-3 and Pax-7, resulting in neural plaque formation. This plate folds to form the neural tube, leaving at the cephalic and caudal ends an orifice called anterior and posterior neuropore, failure in these closures can cause anencephaly, craniorachisis, meningoceles and dysraphy among other anomalies (17). The closure of the neural tube will end around the 28th day of gestation so at this time the pregnant woman with a regular menstrual cycle of 28 days would be perceiving a delay of two weeks and in other cases she would not even be suspecting a pregnancy, so, when the doctor prescribes

folic acid the closure of the neural tube could have already occurred and the defects associated with it will already be present in the embryo. For this reason, the consumption of preconceptional folic acid is preponderant, either by medical prescription in planned pregnancies or by the fortification of foods of mass consumption as a public health measure (18).

The purpose of this reflection is to evaluate the need for folic acid prescription to maintain reproductive health. In the case of pregnant women, the aim is to evaluate the relevance of folic acid supplementation when the first 28 days of gestation have passed and when the neuropores have completely closed, understanding that, although the prevention of congenital defects derived from failures in the closure of the neural tube is one of the factors for which folic acid supplementation is most performed in pregnancy, There are other equally important aspects that should not be ignored and are related to procreation. On the other hand, the possibility of negative interference of an over-bioavailability of folic acid in pregnant women and in the embryo/fetus is analyzed.

2 DEVELOPMENT

Folic acid is vital for DNA synthesis and methylation through the metabolism of one carbon (C1) (19), therefore, it is essential for cell division during embryonic development. During pregnancy, folate requirements increase from 400 to 600 µg/day to ensure fetal growth, so the WHO recommends supplementation in this population group (20).

In cattle and goat models, adequate folic acid supplementation has been shown to induce a significantly higher blast production rate, reduced cytoplasmic levels of reactive oxygen species, and adequate regulation of transcripts for folate transporters (FOLR1) and the enzyme methionine synthase (MTR). key to the folate-methionine cycle (21,22).

Regarding the action of folic acid on neurulation, folate-dependent pathways and gene expressions such as the FOLR1, VANGL2 and WNT/PCP pathway (23), which morphologically contribute to the extension and convergence of neural folds, an action necessary for the neural tube to be formed24. In mouse models with folate deficiency, genes related to neural tube damage have been identified, these genes are VANGL2, as the central gene, and CELSR1, PTK7, SCRIB1, as genes associated with VANGL2 (24-25).

Alterations in neural tube closure appear to have a hereditary component, whose genomic alterations are related to familial recurrence at the chromosomal level. However, it should be noted that there are additional environmental factors that have a negative influence on neurulation (26,27). Additionally, folic acid not only plays an important role in the development of the nervous system, but also in other organs. By the third week of gestation,

the differentiation of the cells of the visceral extraembryonic mesoderm occurs, from which the precursors of blood and blood vessels are formed, therefore, at this point folic acid is fundamental in the formation of blood cells due to the high requirement of mitotic division and high synthesis of nucleic acids required in the development of the hematopoietic and cardiovascular systems (28,29).

Folic acid has an influence, together with micronutrients such as iron, on the weight of the newborn (30). Pregnant women who do not have a fortified diet destabilize the fetus's requirement for necessary folates, leading it to refocus and prioritize methylation to vital organs, so that they unbalance areas of body fat and total size, leading the newborn to an appearance of infant wasting 31. Additionally, folic acid deficiency influences the cognitive state that the individual may have in their childhood stage, studies show that children treated with folic acid beyond the first trimester intrauterine had higher scores than children treated with placebos in the gestational stage (32).

It is theorized that folic acid deficiency increases homocysteine levels, high concentrations of which can induce damage to the vascular endothelium of the developing placenta, additionally it can induce apoptosis of human cytotrophoblast cells, which could affect trophoblast invasion and placental development, inducing hypertensive disorders in pregnancy (33,34,35).

Folate deficiency is common in pregnant women who are not supplemented, the increased demand for this vitamin influences the synthesis of purine nucleotides and thymidine to reduce DNA replication in the erythropoietic cell line, preventing optimal maturation of the erythrocyte precursors, which die and the rest have an abnormal size. characteristic of megaloblastic anemia (36).

As for pregnant women with comorbidities, whose pharmacological prescription may have an interaction with folic acid, the use of anticonvulsants in women with epilepsy or associated diseases stands out, in studies with murines dosed with valproate it has been shown that the gene expression of folate transporters is decreased37. On the other hand, cancer treatment in pregnant women with methotrexate may trigger the inhibition of synthetase and dihydrofolate reductase, blocking folate metabolism and therefore problems associated with DNA synthesis (38).

Although the importance of acid during pregnancy has been widely studied, there is scientific evidence that supports that its role in reproduction is broader, influencing the formation of female and male sexual gametes. For example, in bovine models Folic acid supplementation appears to be a promising factor for improving bovine embryo production if used with care, as folic acid concentration is an important factor, especially in oocytes with

impaired quality (21). In goat models, the effect of folic acid supplementation on the cells that are part of the oophore cluster has also been demonstrated, evaluating markers of cluster expansion (PTX3 and PTGS2) which indicates a higher degree of maturation, and therefore, an active folate-methionine cycle in this process (22).

The possible epigenetic flaws that may occur in a gamete will not only affect the developing embryo but also its offspring, affecting the increased risk of developing diseases in adulthood, such as hypertension, diabetes, heart disease and obesity (39,40).

Sperm quality depends on genetic and environmental factors, including smoking, the consumption of some drugs and nutritional aspects such as folic acid deficiency (41,42). In murine experimental models, folic acid deficiency has been shown to directly induce a higher rate of sperm fragmentation and a subsequent reduction in the pregnancy rate (43). This is explained by the fact that folic acid deficiency delays the processes of sperm meiosis, evidencing an increase in cases of de novo mutations and direct implications for the general health of murines, the effects of which were extrapolated to their offspring (44,45). Folate deficiency is associated with failures in genes such as the h19 gene, which would have consequences in the formation of non-coding RNA, essential for the development of micro-RNAs (46). Another gene that is affected by folate deficiency is the Rad54 gene whose protein expression is responsible for genetic recombination, mainly performing translocation and redistributing DNA strands (47).

Although it is known that folic acid is a water-soluble vitamin and has a saturable system, therefore, it will hardly produce toxicity, there is some research that states that excess consumption of folic acid during pregnancy can have negative consequences on the pregnant woman and the embryo/fetus. Studies in murinos have shown that both deficiency and excess folic acid supplementation delay neurogenesis of the cerebral cortex, which are accompanied by behavioral abnormalities, it has also been indicated that excess folic acid can activate β-catenin through the suppression of PP2Ac demethylation (48,49,50). Regarding the association between autism and folic acid excess, there are currently no conclusive results on this topic and more studies (51)

3 CONCLUSION

Folic acid supplementation is necessary during the preconception period and throughout pregnancy for the optimal development of the embryo/fetus and the good health of the pregnant woman. The adequate bioavailability of folic acid guarantees an ideal gametogenesis, as well as allows the optimal growth of embryonic tissues, placental tissues and some reproductive organs of the pregnant woman to carry out a successful pregnancy.

Additionally, folic acid acts as a protective factor against some diseases such as preeclampsia and megaloblastic anemia. Although there are studies on the negative influence of excess folic acid during pregnancy, scientific evidence is not sufficient, so it is recommended to design research projects that, with all the rigor of the case, can contribute to better elucidating this aspect.

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