Folic acid in pregnancy

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Abstract

Folate (vitamin B9) is one of thirteen vital vitamins and is found in dietary products, while folic acid is the synthetic supplement used to fortify foods with. Both are metabolically inactive and through an enzymatic process mediated by MTHFR become active. Active metabolites have a key role in the DNA methylation process. Due to genetic polymorphisms of the MTHFR gene, impairment of folate activation is common as 60% of the population are heterozygous and 25% homozygous for this. Pregnancy complications that are related to folic acid deficiency includes primarily neural tube defects, as studies suggest a 72% protective effect of folic acid supplementation. An inadequate supply of nucleotides to neuroepithelial cells and/or neural fold retardation and disturbed methylation are possible pathogenetic mechanisms. A possible link between folic acid deficiency and other pregnancy complications such as congenital heart disease, preeclampsia, intrauterine growth restriction, recurrent pregnancy loss, placental abruption, preterm labour and multiple pregnancy has been reported. Folic acid daily intake in pregnant women is 400 μg received from fortified food and vitamin supplementation to decrease risk of neural tube defects by 50%. In high risk pregnancies (previously affected) this dose is recommended for 1–3 months prior to conception.

Keywords folate; folic acid; folic acid deficiency; neural tube defects

Folate (B9), folic acid metabolism, actions

Folate or vitamin B9, is a compound based on folic acid structure, and is considered one of thirteen vital vitamins. It cannot be synthesized de novo and it is obtained from dietary products (green vegetables, egg yolk, liver, citrus). Folic acid is the synthetic dietary supplement administered as part of enriched foods or vitamins. Both substances are metabolically inactive and require a series of enzymatic processes to become active.

Conversion to dihydrofolate (DHF) and tetrahydrofolate (THF) catalyzed by DHF reductase (DHFR) is the first step, followed by conversion to L-methylfolate by methylene-tetrahydrofolate reductase (MTHFR). This conversion allows gut absorption and liver transfer and storage of this active metabolite. Approximately 2/3 are protein-bound (mainly albumin) while 1/3 is protein-free. Folate has a 50% lower bioavailability compared to folic acid as 1 μg of dietary folate equivalents equal 0.6 μg of folic acid in fortified foods or 0.5 supplement taken.

A close association between folate and vitamin B12 exists as deficiency of either one leads to same haematological changes. Folate is substrate and vitamin B12 a co-enzyme in the formation of 5,10 methylene-tetrahydrofolate which is involved in thymidylate synthesis.

This metabolite provides methyl donations during DNA methylations and homocysteine metabolism regulation.

Folate catabolism starts with cleavage of folylpolygluthate and subsequent cleavage products enter the glomerulus or biliary duct. Most cleavage products are re-absorbed either in the proximal renal tubule or in the small intestine.

Genetic polymorphisms

Genetic polymorphisms are common, as about 60% of population are intermediate metabolizers or heterozygous for polymorphism of the MTHFR enzyme and 25% are homozygous for the same polymorphism, thus impairing the conversion of inactive folate to active L-methylfolate.

Pregnancy complications

i. Neural tube defects (NTD)

Folic acid intake at the time of conception is known to reduce the incidence of neural tube defects (NTD) in the fetus, since the early 1990s. Supplementation with folic acid showed a reduction of recurrence of NTD from 5.9 to 0.5%. A randomized double-blind prevention multicenter study recruited 1817 women at high risk for NTD and allocated them to folic acid supplementation, another vitamin supplementation or no supplementation. Results showed a 72% protective effect of folic acid supplementation on NTD (RR 0.28, 95% CI 0.12–0.71), while other vitamins had no protective effect at all (MRCVitamin Study Research Group 1991). Another randomized trial tested treatment efficacy by randomizing women to folic acid administration 0.8 mg daily or trace-element vitamin for the month prior to conception until the second missed menstruation. Congenital malformation rate was significantly higher in the trace-element group than the folic acid group (22.9 per 1000 vs 13.3 per 1000, $p = 0.02$). There were 6 NTD cases in the trace-element group compared to none in the folic acid group. Lack of folic acid results to an inadequate supply of nucleotides to neuroepithelial cells, which decreases their replication and neural fold retardation or disturbed methylation during cranial neurulation are the possible mechanisms involved in NTD development.

ii. Congenital heart disease (CHD)

A possible correlation between decrease folate concentration and congenital heart disease is reported, as there is correlation between MTHFR mutations and CHD. An association between MTHFR C677T polymorphism and CHD has been reported by a large systematic review of Chinese pediatric populations. Several case-control studies reported conflicting reports, as a study by Botto et al., associated folate consumption with a significant reduction of CHD (septal defects and conotruncal defects), while Werler et al., found no significant association between the two. Overall, it is possible that this association exists, but larger studies are required. The possible mechanism for this effect is via the regulation of homocysteine metabolism, which affects the cardiac neural crest cell migration.

iii. Megaloblastic anemia

Folate decrease becomes clinically evident when erythropoiesis is affected, which usually takes 3–4 months as erythrocyte

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lifespan is 120 days. Megaloblastic changes in bone marrow include formation of macrocytes which leads to increased mean cell volume and neutrophil hyper-segmentation (increased number of lobes). Decreased hematocrit, hemoglobin and erythrocyte concentration are all evidence of megaloblastic anemia, which leads to weakness, fatigue, headaches, irritability and palpitations.

iv. Preeclampsia, intrauterine growth restriction

Maternal hyper-homocysteinemia has been linked to pre-eclampsia but studies report conflicting results. Increased homocysteine levels at early second trimester are associated with increased risk of developing non-severe preeclampsia, while other studies suggest that there is a non-significant difference between pre-eclamptic and controls. Various prospective cohort studies conducted among singleton pregnancies at early second trimester, reported increased serum folate and decreased plasma homocysteine to be associated with a decreased risk of preeclampsia development (OR 0.37, 95%CI 0.18–0.75). Folic acid has a regulatory role in placental trophoblast development and specifically in terms of extra-villous trophoblast invasion, vascular density and matrix metalloproteinases secretion, following placental explants cultured in folic acid at 7 gestational weeks.

v. Placental abruption

A possible association between hyper-homocysteinemia and placental abruption is present, as there is a non-significant difference between controls and abruption cases.

vi. Recurrent early pregnancy loss

Association with early pregnancy loss and hyper-homocysteinemia has been reported by case-control studies that assessed serum homocysteine levels (33% vs 14% respectively). Serum homocysteine of 18 mmol/L or more has been linked to an increased risk of early pregnancy loss.

vii. Preterm labour, birth weight

Several studies assessed a possible association between folic acid deficiency and preterm birth. Observational studies suggest that low serum folate is associated with shorter duration of pregnancy. A study that determined maternal and umbilical homocysteine levels concluded that neonatal weight and gestational age are inversely related to maternal homocysteine levels. A prospective study assessed infant birthweight and folate intake (1 mg daily) and concluded that there is a small but significantly positive association between the two, but folate intake remains a weak predictor of infant birthweight. A large prospective observational trial of 34,480 women, concluded that pre-conceptional folic acid supplementation for more than 1 year, is associated with a significant reduction in spontaneous preterm birth rate (HR 0.22, 95%CI 0.08–0.61), that remained unchanged after adjustment for confounders. Possible mechanisms of preterm birth prevention remain largely uncertain, but as studies show, the most likely pathophysiological mechanism involved is alteration of immune response to inflammation. Folate deficiency is linked to decreased response of T-lymphocytes and decreased antibody production to circulating antigens, therefore increasing susceptibility to infections.

viii. Multiple pregnancy

Women that receive peri-conceptional folic acid supplementation are considered at higher risk of multiple pregnancy. A population-based case-control study by Czeizel et al., has associated folic acid supplementation to multiple pregnancy as 0.78% of those that do not receive and 1.52% of those that receive supplementation (OR 1.80; 95%CI 1.14–2.85).

Another population-based study has reported similar findings (OR 1.59 95%CI 1.41–1.78) but following exclusion of IVF pregnancies, there was no significant difference (OR 1.02; 95%CI 0.85–1.24).

Side effects

Masking of pernicious anemia (B12 deficiency) was a concern raised during folic acid supplementation, but diagnosis of this condition should be based on B12 measurement and not haemoglobin levels. Cancer development and primarily colorectal cancer was another possible side effect, but as studies showed there is not increased risk associated with folic acid.

Folate requirements indicators

Several indicators have been proposed to identify folate deficiency:

i. Erythrocyte folate: It relates to tissue stores and provides information on long-term status but not recent status. A cut-off limit of 305 nmol/L (140 ng/ml) has been proposed, as studies showed that all patients with megaloblastic anemia had values less than that.

ii. plasma homocysteine: Increased levels are found in folate deficiency and is considered as a sensitive indicator of folate status. A cut-off limit of 12–16 μmol/L has been proposed, as it is not a specific marker due to the influence by vitamin B12, B6, age, gender and genetic polymorphisms.

iii. serum folate: Decreased levels (less than 3 ng/ml) are considered the first evidence of deficiency and is considered a sensitive indicator of dietary folate but does not distinguish between transient and chronic deficiency.

iv. urinary folate: It is not a sensitive indicator as daily excretion in urine varies considerably.

Recommendations

According to the NHANES II study, mean folic acid intake in the non-pregnant state is 207 μg/day exceeding the threshold of 180 μg/day, while 90% of pregnant women consumed less than the 400 μg/day threshold. The Institute of Medicine (IOM) has recommended that 400 μg of folic acid daily received from fortified foods, vitamin supplementation or both are required during pregnancy to reduce the risk of NTD by 50%.

Median intake prior to food fortification, was 250 μg/day and approximately 80–100 μg/day was added following this decision (Institute of Medicine, 1998). Since most pregnancies are unplanned, high risk patients (history of previously affected pregnancy) are advised to receive this dose during the peri-conceptional period (1–3 months prior to pregnancy) in order to reduce risk of NTD. ◆

FURTHER READING

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