Niger J Paediatr 2021; 48 (2):88– 92

ORIGINAL

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# Folic acid and brain function in childhood

DOI:http://dx.doi.org/10.4314/njp.v48i2.5

Accepted: 21st February 2021

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**Abstract:** Folic acid supplementation does not only prevent neural tube defects in the foetus but is an essential ingredient in the growth and development of the cerebral cortex. This micronutrient promotes the thickness of the cerebral cortex; the extent of the thickness being directly proportional to the intelligent quotient, neurocognitive and psychological output of the child. Children with thin cortices are prone to poor cognitive performance, autism and psychiatric disorders such as depression.

Folic acid supplementation in the first three months of pregnancy largely protects against neural tube defects; studies have shown that children whose mothers take folic acid supplement throughout pregnancy exhibit relatively higher levels of emotional intelligence

Nevertheless, in spite of long-standing recommendations that women of child-bearing age take folic acid to protect against neural impairment, a large proportion do not comply; less than half of the world's population lives in countries that require folic acid fortification of grain products. A large portion of pregnant women in poor world countries do not attend antenatal care hence have no access to prescription of essential haematinic/folic acid.

It is recommended that all women who are either planning or capable of pregnancy take a daily supplements containing 0.4 - 0.8 mg (400 -800 µg) of folic acid.

Fortified foods like some breads, juices, and cereals contain adequate folic acid; others are leafy green vegetables, like spinach, broccoli, and lettuce beans, peas, and lentils. Fruits like lemons, bananas, and melons are also rich sources of folate.

There is need for more advocacy regarding antenatal care of pregnant mothers with emphasis on folate supplementation before and throughout pregnancy, to boost the intellectual and psychological capacity of children into adulthood.

## Introduction

Folate, labelled as vitamin B9, is found naturally in foods. Folic acid is the manmade version (synthetic and more highly bioavailable form of the naturally occurring folate)sold as supplements and added to fortified foods. Folate and folic acid have the same effects hence, in this communication the terms - folate and folic acid, will be used interchangeably.

Rich sources of folic acid and folate include: Fortified and enriched products, like some breads, juices, and cereals; others areleafy green vegetables, like spinach, broccoli, and lettucebeans, peas, and lentils. Fruitslike lemons, bananas, and melons are also rich sources of folate. Folic acid is available in tablet form of 5mg denomination.

Folate is a water-soluble B-complex vitamin that supports some of the body's most vital functions, including the production of DNA and neurotransmitters, and the detoxification of cells. Folic acid promotes cellular growth and maturation of red blood cells.

Folic acid plays an important role in cell division, and synthesis of amino acids and nucleic acids and is therefore essential for growth. It is necessary for normal development of the foetal spine, brain and skull, in particular during the first four weeks of pregnancy.[1-4]

Deficiency of folic acid is associated with reduced body growth, energy, and megaloblastic anaemia among others.[1-5]

It has been well established that preconceptual exposure to folic acid protects the foetus against neural tube defects (NTD) including anencephaly which occur during the third and fourth week of pregnancy, before the woman knows she is pregnant. Other studies indicate that periconceptual use of folic acid reduces risk for other congenital malformations, including oral clefts.[6] In addition, folic acid supplementation has been associated with clinically significant reductions in risk

of miscarriage, stillbirth, preterm birth, and neonatal mortality.[6]
Folic acid fortification not only protects developing babies against certain birth defects but also supports healthy brain performance through the teenage years. There is an association between prenatal folic acid exposure, maturation of the brain's cortex, and the risk of psychiatric disorders in youths 8 to 18 years of age born before, during, and after full implementation of folic acid fortification of grain products between 1996 and 1998.[7]

During pregnancy the rate of cell division and erythrocyte formation increases dramatically as the uterus enlarges, the placenta develops, maternal blood volume increases and the embryo develops into a foetus.[3] In addition, folate is transferred from the mother to the growing foetus increasing the demand for folate beyond her sole requirements.[2]
Considering this evidence and recognizing that pregnancies are not always planned, the requirement for folic acid in women of child bearing age and during pregnancy has become well established and internationally recognized.

*Neural tube defect world wide*

Following a global survey on neural tube defects from January1990- July 2014 involving 75 countries, the regional frequencies of the defect were: Africa, 11.7; Europe, 9; the Americas,11.5; and South-east Asia, 15.8 per 10,000 births.[1, 8] The prevalence of neural tube defect in Nigeria is 22 per 10,000 births. Some babies with severe NTD are stillborn or do not survive long after birth. In underdeveloped countries pregnancies are not booked, a majority of deliveries take place outside hospitals, stillbirths and early neonatal deaths are not recorded, therefore published figures on the prevalence of NTD may appear deceptively lower than what is recorded.
Studies have reported a decreased risk of neural tube defects including malformations of the spinal column (spina bifida) and the skull (anencephaly) is associated with both increased maternal folate intake and higher maternal red blood cell folate concentration (greater than 906 nmol/L).[7]
Since the link between folate deficiency and neural tube defect has been so well established, the target of this review article is largely on the impact which folate has on the cerebral cortex hence its influence on neurocognitive and behavioural performances in childhood.

*Neurochemistry*

Folic acid is a carrier of hydroxymethyl and formyl groups and is involved in the synthesis of purines and thymine, required for the formation of DNA. The conversion of homocysteine to methionine requires the enzyme methionine synthetase and uses methyltetrahydrofolate as a methyl donor and vitamin B12 as a cofactor. Mothers of children with neural tube defects had significantly elevated homocysteine levels.[9,10] The defect may be related to abnormalities in the activity of the enzyme methionine synthetase. Methionine synthetase is critical for methylation in a number of biologic processes, including the production of myelin basic protein and DNA biosynthesis. Both folate and B12 are required as cofactors for methionine synthetase.

*Neuroanatomy*

A comprehensive study in the USA on folic acid fortification of grain products examined the association between increased foetal exposure to folic acid and subsequent cortical development. Measurements of cortical thickness was obtained from magnetic resonance imaging scans because it provided a clinically relevant developmental marker. Eryilmaz H *et al*.[11] evaluated three independent MRI cohort of 8 to 18 year old youths (n=292) in association of prenatal exposure to varying quantities of folic acid consumption with subsequent cortical development through adolescence. Variation in foetal exposure to folate subsequently influences brain development during the formative years preceding late adolescence and early adulthood.[11] Folic acid plays a role in determining cerebral cortical thickness; after the brain reaches its full thickness, the cortex begins to thin in a selective pruning process. The thickness is found to be greatest with adequate folic acid intake and wanesproportionally as the folic acid intake by the mother declines. Folic acid fortification is associated with slower thinning of the brain cortex, and this delayed thinning has been associated with higher intelligence, whereas accelerated thinning has been associated with low level of school performance, schizophrenia, and autism.[11-17]
Among a Norwegian cohort of mothers and children, maternal use of folic acid supplements in early pregnancy was associated with a reduced risk of severe language delay in children at age 3 years.[16]

These findings suggest that folate insufficiency in early pregnancy has long-lasting effects on brain development and is associated with poorer cognitive performance in school age children. This study highlights the importance of folic acid supplementation during pregnancy and, because foetal brain development takes place throughout the pregnancy, and not just during the first trimester, suggests that the benefits of folic acid supplementation may extend beyond the first trimester.
In addition, more recent data indicate that periconceptual use of folic acid may have other important benefits for the developing brain. For example, women who consume the recommended daily dosage of folic acid during the first month of pregnancy may have a reduced risk of having children with an autism spectrum disorder.[16-18]

*Folic Acid and Severe Depression in Teenagers*

Ground breaking research on teens diagnosed with severe depression has found that many for whom therapy, medication, and hospitalization have not worked are suffering from metabolic deficiencies that prevent their

body from properly converting and absorbing folic acid. From a study of 33 patients diagnosed with treatment-resistant depression, twenty-one suffered from a metabolic deficiency, with the most common deficiency being cerebral folate. Treatment with folinic acid yielded dramatic improvement.[19,20] In neonates, infants, children, and adolescents, inborn errors of folate transport and metabolism are associated with a variety of overlapping syndromes which are influenced by age of clinical presentation. These include developmental delay, cognitive deterioration, motor and gait abnormalities, behavioural or psychiatric symptoms, seizures, signs of demyelination or failure of myelination, and vascular changes seen on magnetic resonance imaging or postmortem examination.[18-20]

*Folate Vs Antiepileptic drugs*

There has been a concern that folic acid may be too low in persons with epilepsy taking some antiepileptic drugs (AEDs). Low serum and red blood cell levels of folic acid in women of childbearing potential increase the risk of foetal birth defects.[6,9] A convincing argument now develops that routine folic acid supplementation is important for women receiving AEDs. Women receiving some AEDs are at risk for low levels of serum and red blood cell folic acid. Serum and red blood cell folate are reduced in up to 90% patients receiving phenytoin, carbamazepine, or barbiturates.[9,20-22] AEDs that do not induce cytochrome P450 enzymes are not associated with low levels of folic acid. Lamotrigine (LTG) and Sodium Valproate have weak folate properties in vitro, had no effects on serum or red blood cell folate. Based on currently available information, it seems prudent to ensure that pregnant women with epilepsy receiving AEDs, particularly enzyme-inducing AEDs, receive adequate folic acid. For most individuals, this is best accomplished by providing a dietary supplement. Supplementation can be provided by prescription-strength folic acid tablets (1 mg each) or as part of a multivitamin supplement. Most multivitamins contain 0.4 mg of folic acid. Over-the-counter prenatal vitamins contain 0.8 mg folic acid, and prescription prenatal vitamins contain 1 mg of folic acid.

*Recommendations on folate intake*

There is an age long recommendation that women of child-bearing age take folic acid to protect against neural tube defects, especially in the event of unplanned pregnancy but most women who are capable of pregnancy do not take prenatal folic acid supplements.[23] Less than half of the world's population lives in countries that require folic acid fortification of grain products. Women at risk of low folate status include those with lower socioeconomic status; IDP camps, and those with limited or uncertain availability of nutritionally adequate and safe food. Due to ignorance and poverty, women in the underdeveloped and developing world countries rarely book for antenatal care; they prefer to patronise Traditional Birth Attendants and churches for care and delivery.[24] Such women therefore have no access to pregnancy-related prescription of haematinics/folic acid.

It is mandatory to promote fortification of food with folate supplementation for all women who could become pregnant. Folicacid during pregnancy is safe for both mother and foetus, cheap, and readily available. This awareness may help compel its wider use.

Research has shown that folic acid levels are essential in the very early stage of foetal development, which has lead the Centres for Disease Control and Prevention (CDC) to recommend that women take the recommended daily dose of folic acid for at least a full month prior to conception and throughout the entirety of the first trimester in order to optimize its preventive effects. While it is currently recommended that folic acid supplements be started at least one month prior to pregnancy and maintained throughout the first trimester. There appears to beno consistent recommendations regarding the need to maintain folic acid supplementation beyond the first trimester.[25]

More recent survey has shown that children whose mothers took folic acid supplement throughout pregnancy demonstrated higher levels of emotional intelligence and resilience. Additionally, the level of folic acid in the mother's blood towards the end of pregnancy is a good predictor of children's resilience and emotional intelligence. It appears taking folic acid supplement in the first three months of pregnancy is largely important in spinal development but there are potential psychological benefits for the child if supplements are taken throughout the pregnancy.[26]

It is recommended that all women who are either planning or capable of pregnancy take a daily supplement containing 0.4 - 0.8 mg (400-800 µg) of folic acid.[27]

Folate toxicity

While the healthy dose of folic acid per is 400 micrograms, adult men and women adults who consume up to 1000 micrograms a day stand the risk of developing colon and prostate cancers.[28] Generally the incidence folic acid toxicity should be very low since the folate is water soluble and therefore can be easily eliminated in the urine. This risk of toxicity has not been reported in children.

It is possible to determine the serum and red cell levels of folic acid. The use of liquid chromatography-tandem mass spectrometry to measure serum folate has been recommended for population monitoring as it allows a more accurate and reproducible measurement.[29]

## Conclusion

Foetal exposure to folic acid is essential in cerebral cortical development in children. Prenatal folic acid supplementation is therefore necessary for appropriate neurodevelopment during childhood and adolescence. If folate is deficient there is inadequate and poor formation of the white and graycortical mater hence the child's cognitive development is impaired. Folate supplementation also reduces the risk of early-onset schizophrenia, autism and

speech disorder. Even with wide spread recognition of the need for folic acid to prevent neural tube defects, it is still not widely used in the general population. There is a continuous need for a strong advocacy for prenatal folate supplementation for all women expected to become pregnant in order to save young brains.

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