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Relation between Folic Acid and Neural Tube Defect

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Abstract

Neural tube defects (NTDs) are common complex congenital malformations resulting from failure of the neural tube closure during embryogenesis, a lot of studies established that folic acid supplementation decreases the prevalence of NTDs, this report summarizes some of these studies, which have led to the current situation in which all women capable of becoming pregnant should consume 400 micrograms of folic acid/day for the purpose of reducing this risk. The folate-NTD relation represents the only instance in which a congenital malformation can be prevented simply and consistently. Nevertheless, several research gaps remain: identification of the mechanism by which the defect occurs and how folate ameliorates it, characterization of the relative efficacy of food folate, folic acid added to foods, and folic acid by itself; delineation of the dose-response relations of folate and NTD prevention.

Introduction

Insufficiency of folate during early pregnancy is associated with increased risk of birth defects. Women of a particularly poor population subgroup manifested severe anemia during pregnancy, early abortions, and malformed births. The vitamin folate has been discovered and purified in 1945, during the first 2 decades after folate discovery, large doses of folic acid have been used to correcting anaemia and/or neurological manifestations. (1)

Folate is a generic term for a water-soluble, B-complex vitamin that serves as an essential coenzyme in single-carbon transfers in the metabolism of nucleic and amino acids and thus fills an important function in purine and pyrimidine metabolism. Dietary folate (mainly as 5-methyltetrahydrofolate) serves as methyl donor in the cells. It provides a methyl group to homocysteine that is converted to methionine simultaneously releasing tetrahydrofolate. Tetrahydrofolate is further converted to be used for nucleotides synthesis (mainly from for myltetrahydrofolate derivatives). The folate cycle (exists in the cytosol, mitochondria, and cell nucleus) ensures the transfer of C1-units (glycine, serine, and format) between these cell compartments, its metabolism is particularly active during cell division such as in pregnancy and early childhood. The congenital defects are known to be sensitive to low folate at early pregnancy. While folic acid (a monoglutamic acid) is the oxidized and most active form of the vitamin; found rarely in food, it is the form used in vitamin preparations and food fortification. The distinction between food folate and folic acid is important because of differing bioavailability (i.e., food folate is only about half as available as folic acid consumed on an empty stomach.)

Neural-tube defects and congenital heart defects are typical congenital abnormalities with very early (prenatal) onset and defect condition, thus in general there is no or only limited chance for complete recovery. Therefore prevention is the only unique medical solution, and fortunately a breakthrough occurred in the prevention of neural-tube defects by periconceptional folic acid (FA) or folic acid-containing multivitamins (MV.). (2)

Neural-tube defect (NTD) is the most frequent and the most tragic congenital abnormality of the central nervous system. The brain and spinal cord develop from the neural-tube which is formed by dorsal folding of the neural plate after the 15th postconception day. The fusion of this folding proceeds in the cranial and caudal directions and is normally completed in humans between the 21st–26th postconception day in the cranial pole and between the 23rd–28th day in the caudal pole, respectively. These periods therefore correspond to the critical period of cranial pole defect: anencephaly and caudal pole defect: spina bifida. (2, 3)

The relation between folate and neural tube defects (NTDs), first suggested a little >50 year ago, has become recognized as a result of a large number of clinical investigations. In the first place, the relative importance of congenital malformations in general has increased as other major causes of fetal and infant morbidity and mortality have come under control. Furthermore, NTDs are common and they represent a major public health problem by virtue of their mortality, morbidity, social cost, and human suffering. Finally, and perhaps most importantly, that the maternal folic acid supplementation prevents a substantial proportion of NTDs, but the precise mechanism of folic acid role in neural tube defects is not clear. Current thinking includes considering a role for the enzyme methionine synthase and several genetic defects. (4)

Methods

This study began in 1997 and ascertains participants from 10 population-based birth defects surveillance systems, the researchers studied 243 women with pregnancies complicated by some forms of birth defect(s). (5)
The patients were identified by medical diagnostic tests as having a fetus with some types of congenital anomalies.The patients were then referred to at least three consultant specialists for final confirmation of congenital anomalies. Following this, they were then offered termination of pregnancy according to the current national guideline for the termination of pregnancy. (5)

They compared two groups:
Group I: 175 women who had used folic acid on a daily-based dose of 400 microgram until the end of their first trimester of pregnancy.
Group II: 68 women who never used folic acid during their pregnancies.

And another group of women (118) with normal pregnancy was also taken to assess the current situation of folic acid use in general population of pregnant women.(5)

Results

The mean age of mothers was 28.6 years (range: 14–44 years). The majority of them (65%) had lower socioeconomic status.

The prevalence rate of NTDs among pregnant women who were referred for therapeutic termination of pregnancy was 24.7 percent. The occurrence of NTDs was 16.1 percent (CI 95%: 11.31–22.15) and 47.1 percent (CI 95%: 35.67–58.76) in group I and II, respectively.

Consumption of folic acid prevented NTDs by 79 percent (Odds Ratio = 0.21, CI 95%: 0.12–0.40) and 94 percent (Odds Ratio = 0.06, CI 95%: 0.03–0.15) compared to pregnancies complicated by other anomalies and normal pregnancies, respectively.

Other anomalies including hydrops fetalis, hydrocephaly, Down syndrome, and limb anomalies did not have any significant association with the use of folic acid before/during the pregnancy

Type of anomaly	Used		Did not use	
	n	% (CI 95%)	N	% (CI 95%)
Neural Tube Defects	**28**	**16.09 (11.31–22.15)**	**32**	**47.06 (35.67–58.76)**
Hydrops fetalis	**20**	**11.49 (7.52–16.99)**	**6**	**8.82 (4.11–17.94)**
Hydrocephaly	**26**	**14.94 (10.35–20.88)**	**8**	**11.74 (6.08–21.53)**
Down syndrome	**16**	**9.19 (5.71–14.33)**	**5**	**7.35 (3.18–16.09)**
Limb anomalies	**20**	**11.49 (7.52–16.99)**	**2**	**2.94 (0.81–10.1)**
Others	**65**	**36.78 (30.33–44.51)**	**15**	**22.05 (13.85–33.26)**

Discussion

The study show association between folic acid use and occurrence of NTDs in a group of women referred for therapeutic termination of pregnancy.

In the folate-sensitive NTDs, the development of the central nervous system is arrested during early pregnancy and the neural tube remains open. Live births with spina bifida have high morbidities and mortalities compared with healthy children.(6) The risk of NTDs is particularly high in women who already experienced this outcome in a previous pregnancy (recurrent NTDs).(7) The Centers for Disease Control and Prevention (CDC) advised women at high risk by virtue of a previous NTD pregnancy to plan subsequent pregnancies so that they could ingest folic acid at a level of 4 mg daily, beginning before conception and continuing through the first trimester of pregnancy, also in 1991, the MRC study in women with a previous pregnancy affected with NTD found that a high-dose folic acid (4 mg/d) can reduce the risk of recurrent NTD by 72% [relative risk (RR) =0.28, 95% confidence interval (95% CI): 0.12–0.71].(7)

In a primary prevention RCT (1992), supplemental 800 µg/d folic acid or multivitamins without folic acid was administered to 4,753 pregnant women, and have been improved that all NTD cases could be prevented in the women who received 800 g/d folic acid. The lowest dose of supplemental folate that can prevent all folate-responsive NTDs (cases that can be prevented by folate) has never been established. (8) Observational studies over many years supported the notion that sufficient folate status at early pregnancy reduces neonatal mortality from NTDs. Women of reproductive age are the main target group of all public health interventions aiming at preventing NTDs. Nevertheless, there are still NTD cases that do not respond to folate supplements. (9)

Conclusion

Folate supplementation before and during first pregnancy trimester have protective effect and it's highly recommended for prevention of NTDs and this has been confirmed by several studies. However, the mechanisms underlying folic acid responsive NTDs remains to be elucidated.

References

1. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA 1988;260:3141–5.
2. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. *Au KS, Ashley-Koch A, Northrup H Dev Disabil Res Rev. 2010; 16(1):6-15*
3. Embryology of neural tube development. *Sadler TW, Am J Med Genet C Semin Med Genet. 2005 May 15; 135C(1):2-8*
4. Hibbard BM. The role of folic acid in pregnancy. J Obstet Gynaecol Br Commonw 1964;71:529–42.
5. The National Birth Defects Prevention Study.*Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, Costa P, Druschel C, Hobbs CA, Romitti PA, Langlois PH, Edmonds LD Public Health Rep. 2001; 116 Suppl 1():32-40.*
6. Population-based study to determine mortality in spina bifida: New York State Congenital Malformations Registry, 1983 to 2006.*Kancherla V, Druschel CM, Oakley GP Jr Birth Defects Res A Clin Mol Teratol. 2014 Aug; 100(8):563-75.*
7. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group.*Lancet. 1991 Jul 20; 338(8760):131-7.*
8. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *Czeizel AE, Dudás I,N Engl J Med. 1992 Dec 24; 327(26):1832-5.*
9. Folic acid to reduce neonatal mortality from neural tube disorders.*Blencowe H, Cousens S, Modell B, Lawn J Int J Epidemiol. 2010 Apr; 39 Suppl 1():i110-21.*