Review Article

Folic Acid - Prevention of birth defects

Miriam Gatt, Yves Muscat Baron, Elaine Claire Lautier, Neville Calleja

Abstract

Folate is essential for normal cell division and as intrauterine fetal growth involves a process of rapidly dividing cells, there is a consequent increased requirement for folate at this time. Folate, and the synthetic form folic acid, is thus vital for the early development process of a healthy fetus and there is indisputable evidence that it can significantly reduce the risk of neural tube defects (NTDs). Further ongoing research suggests that folic acid supplementation in pregnancy is also associated with a decreased risk of other birth defects. This review gives an overview of the current literature related to the use of folic acid in the peri-conceptional period and prevention of birth defects, in particular NTDs.

Miriam Gatt* M.D., M.Sc. HSCR (Sheffield)
miriam.gatt@gov.mt
Directorate for Health Information and Research
95, G'Mangia Hill
G'Mangia

Yves Muscat Baron FRCOG, PhD.
Department of Obstetrics & Gynaecology
Mater Dei Hospital
Msida, Malta

Elaine Claire Lautier M.D., M.Sc.
Public Health Sprecialist Trainee

Neville Calleja M.Sc. (Lond.), M.Sc., PhD (Open).
Directorate for Health Information and Research
95 G'Mangia Hill,
G'Mangia

**Corresponding Author*

Keywords

folic acid, neural tube defects, birth defects.

Introduction

It has long been acknowledged that *"a healthy start in life must be a top priority for any society*"(WHO, 1998 p.21).[1] Achieving optimal maternal and infant health is an important goal for all health care systems and is emphasized in the WHO Millennium Development Goals.[2] Today, congenital anomalies are among the major causes of perinatal and infant mortality and morbidity in developed countries.[3] It is known that avoidance of certain environmental exposures, adequate nutrition, folate and other vitamin intake, cessation of smoking and alcohol consumption, prevention and control of maternal infection and disease are among the interventions that may avoid congenital anomalies.[4] Nevertheless, many fetuses still suffer from potentially avoidable birth defects and this is an important area where public health initiatives and interventions can be effective in the primary prevention of congenital anomalies.

This review outlines the current knowledge related to the use of folic acid in the prevention of severe birth defects.

Folate and folic acid

Folate is one of the water-soluble B vitamins; Folic Acid (FA) is the synthetic form of this vitamin and is only minimally different from folate. FA has the advantage of being better absorbed by the body and having a much higher bioavailability than naturally occurring folate.[5]

Being water soluble, folate is easily excreted by the body and is not stored, such that an adequate daily intake is necessary to maintain the required blood levels of this vitamin. The National Institute of Health – Office of Dietary Supplements in the UK[6] gives the daily recommended dietary allowance (RDA) of folate for an adult male or female as 400 micrograms, this requirement increases to 600 micrograms of dietary folate in pregnancy. Folate is found naturally in several

foods including liver, yeast, leafy green vegetables, such as spinach, various fruits including oranges, eggs and beans.[6]

Folate is known to be important for the formation of red and white blood cells, proper development of the fetus and the formation of nucleic acids in DNA (deoxyribonucleic acid) and RNA (ribonucleic acid)[6]. Folates also play an important role in homocysteine metabolism, with folate having a homocysteine lowering effect.[7]

Adequate blood folate levels have been documented to be associated with several beneficial health effects; however, the most notable are the health benefits associated with maternal and fetal health.[8]

Folate and maternal, fetal and perinatal health

Low maternal blood folate levels have long been implicated in increased risk of megaloblastic anaemia necessitating treatment with FA.[9] More recently, low folate levels have been associated with low birth weight;[10] the affect believed to be mediated through plasma homocysteine metabolism, with folate acting to decrease harmfully high homocysteine levels.[11] Low birth weight is associated with poor perinatal outcomes including higher mortality and morbidity as well as long term motor and cognitive disorders[12] and increased risks of cardiovascular and metabolic disease later on in the infant's life.[13]

Bergen et al. (2012)[11] showed that *"women with high homocysteine and low folate concentrations have lighter placentas and lower birth weight by 110 and 124g, respectively"* (p.748). These are significant findings as "*these estimates are of similar magnitude to, for example, smoking, which is a well-established risk factor for impaired fetal growth"* (p.748).

Other adverse pregnancy outcomes that have been associated with low maternal folate include prematurity, pre-eclampsia and spontaneous pregnancy loss,[14] however these associations have not been confirmed.[15]

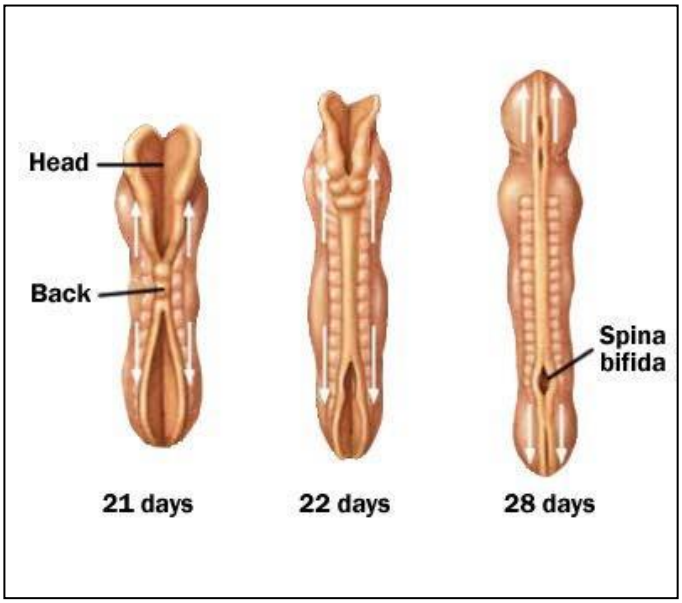
Inadequate maternal blood folate levels have also recently been associated with poorer infant neurodevelopment including language delay,[16] impaired attention function and autism[17]. The results of these studies are, however, conflicting and inconclusive and further research to determine the exact association, if any, is required.

The most significant and widely researched associations of low maternal folate levels have been with the occurrence of certain birth defects namely neural tube defects (NTDs).

Folic acid and neural tube defects

NTDs are major birth defects resulting from inappropriate development of the neurological system in early embryonic growth (Fig. 1) and occur with a prevalence of around 1 in 1,000 births in Europe.[18] The major NTDs encountered are anencephaly and spina bifida, which occur when the neural tube fails to close. These defects are associated with severe morbidity and mortality, causing distress to both the individual and his family and presenting a significant burden to public health.[19]

Figure 1*: Embryonic development and spina bifida (By permission of Mayo Foundation for Medical Education and Research. All rights reserved,* http://www.mayoclinic.org/diseases-conditions/spina-bifida/multimedia/spina-bifida/img-20006705*)*



Obladen (2011),[20] in his paper titled *'Cats, Frogs and Snakes: Early Concepts of Neural Tube Defects',* describes the colourful history of the various beliefs regarding the causation of these defects. He describes how in the past these infants were considered as *'human monsters'*. In the 16th century such defects were attributed to "*imagination, God's glory, God's wrath and demons and devils*" (p.1454); in the 18th and 19th centuries the predominant belief was that these defects resulted primarily from the mother's

imagination and experiences during pregnancy. However, in spite of this generally held idea, some eminent scientists of the time did doubt that imagination would impinge so significantly on the formation of the infant.[20] It was only in the late 18th and early 19th century that the embryogenic formation and closure of the neural tube was described.[21] In the 20th century, several epidemiological studies observed regional and socioeconomic differences in the prevalence of NTDs, implicating the role of environmental factors in the causation of NTDs.[22] It was not until 1965 that folate deficiency was associated with the occurrence of NTDs.[23] Current understanding is that NTDs are associated with folate deficiency and disturbed methylenetetrahydrofolate reductase (MTHFR) metabolism,[24] however, as Blom et al. (2006)[25] describe, "*the case is far from closed*" (p.724) and further research into the causation of NTDs is ongoing.

Evidence of a possible relationship between defective folate metabolism in the mother and embryopathy was first raised in the mid-1960s[23] and the possible role of blood folate deficiency in the occurrence of NTDs was described by Smithells et al. in 1976.[26] In 1981, Smithells et al. [27] published the results of a multicentre, case-control study in which women who had previously given birth to an infant with NTD and were planning to become pregnant again were offered a multivitamin containing, amongst others, 360ug of FA. These women were advised to take the multivitamin at least 28 days prior to conception. Results of this study showed a 4% recurrence rate of infants with NTDs in those women who had no vitamin supplementation as opposed to a 0.4% recurrence in those women who had vitamin supplementation. The authors concluded that "*the most likely explanation is that supplementation has prevented some neural tube defects*" (p.911).

Further corroborating these findings, Laurence et al. (1981)[28] report on a double-blind randomised controlled trial conducted in Wales, which engaged 111 women who had had a previous child with NTD. In this study, it was not a multi-vitamin, but specifically FA that was given to these women. Sixty women were advised to take 4mg of folic acid daily before and during early pregnancy (of these 44 complied while 16 defaulted) and 51 women were given a placebo. The researchers reported that there were no recurrences in those mothers who had complied with treatment (n=44), 2 recurrences in mothers who had not complied (12.5%, n=16) and 4 recurrences in those women taking a placebo (7.8%, n=51); these findings were significant, p=0.04.[28] These studies were followed by a number of others demonstrating the prevention of recurrence of NTDs using FA supplementation.[29-30]

In July 1983, the Medical Research Council Vitamin Study Research Group[31] launched a large randomised double-blind prevention trial involving 33 centres from 7 different countries to determine whether peri-conceptional supplementation (before and until 12 weeks of pregnancy) with FA and/or other vitamins could prevent recurrence of NTDs in women with a history of NTD infants. Results of this landmark trial were published in The Lancet in July 1991. This trial clearly showed that FA had "*a 72% protective effect"* (p.131) for recurrence in those women who had had a previous infant with NTD.[31]

In 1992, Czeizel and Dudas[32] carried out a double blind randomised controlled trial in women planning a pregnancy and *not* having a history of an infant with NTD. The women were randomised to either having a multivitamin supplement (containing, amongst others, 800ug of FA) or a mineral-only supplement starting at least one month before the intended conception. Pregnancy outcomes of the two study groups were evaluated and a significantly lower rate of NTDs was encountered in the group taking multivitamins. None of the 2,394 mothers taking multivitamins including FA had a baby with NTD whereas 6 of the 2,310 mothers taking minerals without multivitamins had a baby with NTD, with p=0.029.[32] In this milestone study, the authors concluded that "*peri-conceptional vitamin supplementation reduced the incidence of a first occurrence of neural tube defects*" (p.1834).
Following these breakthrough findings in the 1980s and early 1990s, a large number of studies further establishing the protective role of FA in preventing NTDs, have been published.[33–35]

Berry et al. (1999),[36] carrying out community-based intervention studies in two regions of China, demonstrated that daily supplementation with 400ug of FA alone could prevent these defects both in areas of high incidence as well as in areas with low incidence of NTDs. The reduction being more marked in the areas of high incidence.

Three Cochrane Systematic Reviews with

meta-analyses examining the relationship between FA and NTDs have been carried out by De-Regil et al. in 2010,[37] Lumley et al. in 2011[38], and De-Regil et al. in 2015,[39] all concluding that peri-conceptional FA has a protective effect against NTDs.

In summary, research has convincingly shown that peri-conceptional FA intake (from at least one month before conception to 12 weeks of pregnancy) can decrease the rate of NTDs by 50% for the first occurrence and up to 70% for recurrence if taken at the correct time,[31,40] giving good scope for action to actively prevent these defects.

To obtain maximum benefits the optimal time of taking FA to avoid preventable NTDs is to start supplementation at least one month before conception until at least one month after as the development of the neural tube occurs early in embryological development.[38] The dose of peri-conceptional FA advised for women to reach the required blood folate status is 400ug daily in women with the lowest risk of NTDs and 4mg daily in high-risk women with a history of NTDs or women with certain chronic disease, including epilepsy treated with anti-epileptic drugs.[41] Recent research also shows benefits of folic acid supplementation for the male partner with a personal history of NTDs.[42]

Folic acid and other birth defects

Ever since the protective influence of peri-conceptional FA supplementation on the occurrence of NTDs was described, interest in possible associations between maternal FA supplementation and the occurrence of other birth defects has grown.[43-44] In an extensive systematic review of studies investigating associations between multivitamins containing FA and various birth defects, Botto et al. (2004) found that peri-conceptional multivitamin use was associated with an *overall* decreased risk of congenital anomalies which was not due solely to the decrease in NTDs.[44] There is evidence that FA may decrease the occurrence of congenital heart defects.[43,45] A European registry-based case-control study by Van Beynum et al.[46] in 2010 analysing birth defects in the Northern Netherlands over a 10-year period (1996 to 2005) showed a decreased risk of all types of congenital heart disease with peri-conceptual FA use. The authors conclude that FA may decrease the prevalence of congenital heart disease by approximately 20%.[46]

There is emerging evidence of a protective role of FA in the prevention of orofacial clefts[47] and abdominal wall defects namely gastroschisis and omphalocele.[48-49] However, these claims have not been conclusively confirmed and remain debatable.[37,39]

Conclusion

Evidence for the protective function of FA in prevention of NTDs, when taken prior to conception and throughout the first trimester of pregnancy, is indisputable. Research showing protection against other birth defects including congenital heart, orofacial clefts and abdominal wall defects is less so, rendering definitive conclusions at this time premature.

Maximising the intake of folic acid in the peri-conceptional period is truly an area where public health action can concretely contribute to the decrease of severe, disabling and potentially lethal NTDs.

References

1. World Health Organisation. Health 21 Targets.; 1998. http://www.euro.who.int/_data/assets/pdf_file/0004/109759/EHFA5-E.pdf.
2. World Health Organisation. Millenium Development Goals. 2015. http://www.who.int/mediacentre/factsheets/fs290/en/.
3. Rosano A, Botto LD, Botting B, Mastroiacovo P, Germany W. Infant mortality and congenital anomalies from 1950 to 1994 : an international perspective. J Epidemiol Community Health. 2000;54(9):660-666.
4. Dolk H. What is the "primary" prevention of congenital anomalies? Lancet. 2009;374(9687):378.
5. Winkels R., Brouwer IA, Siebelink E, Katan MB, Verhoef P. Bioavailability of food folates is 80% of that of folic acid. Am J Clin Nutr. 2007;85:465-473.
6. National Institutes of Health. Dietary Supplement Fact Sheet - Folate.; 2012. http://ods.od.nih.gov/pdf/factsheets/Folate-HealthProfessional.pdf.
7. Clarke R, Homocysteine Lowering trialists Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine : a meta-analysis of the randomized trials. Am J Clin Nutr. 2005;82:806-812.
8. Tamura T, Picciano M. Folate and human reproduction. Am J Clin Nutr. 2006;83:993-1016.
9. Chanarin I, MacGibbon B, O'Sullivan W, Mollin D. Folic-acid deficiency in pregnancy - The pathogenesis of megaloblastic anaemia of pregnancy. Lancet. 1959;2(7104):634-639.

10. Timmermans S, Jaddoe V, Hofman A, Steegers-Theunissen R, Steegers E. Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study. Br J Nutr. 2009;102(5):777-785.
11. Bergen NE, Jaddoe VW, Timmermans S, Hofman A, Lindemans J, Russcher H, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: The generation R study. BJOG An Int J Obstet Gynaecol. 2012;119(6):739-751.
12. Wilcox AJ. On the importance--and the unimportance--of birthweight. Int J Epidemiol. 2001;30(6):1233-1241.
13. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;341(8850):938-941. http://www.ncbi.nlm.nih.gov/pubmed/8096277.
14. Dodds L, Fell DB, Dooley KC, Armson BA, Allen AC, Nassar BM, et al. Effect of homocysteine concentration in early pregnancy on gestational hypertensive disorders and other pregnancy outcomes. Clin Chem. 2008;54(2):326-334.
15. Lassi Z, Salam R, Haider B, Bhutta Z. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes (Review). Cochrane database Syst Rev. 2013;(3):CD006896.
16. Roth C, Magnus P, Schjølberg S, Stoltenberg C, Suren P, McKeague IW, et al. Folic acid supplements in pregnancy and severe language delay in children. JAMA. 2011;306(14):1566-1573.
17. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, et al. Maternal periconceptional folie acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr. 2012;96(1):80-89.
18. Eurocat Folic Acid Working Group. Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe. 2009;44(December). http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf.
19. Sawin KJ, Thompson NM. The Experience of Finding an Effective Bowel Management Program for Children With Spina Bifida: The Parent's Perspective. J Pediatr Nurs. 2009;24(4):280-291.
20. Obladen M. Cats, Frogs, and Snakes: Early Concepts of Neural Tube Defects. J Child Neurol. 2011;26(11):1452-1461.
21. Glaser O. The thoery of autonomous folding in embryogenesis. Science (80-). 1916;44(1136):505-509.
22. Hewitt D. Geographical variations in the mortality attributed to spina bifida and other congenital anomalies. Brit J Prev Soc Med. 1963;17(13):13-22.
23. Hibbard ED, Smithells R. Folic Acid Metabolism and Human Emryopathy. Lancet. 1965;1(7398):1254.
24. Blom HJ. Folic acid, methylation and neural tube closure in humans. Birth Defects Res Part A - Clin Mol Teratol. 2009;85(4):295-302.
25. Blom HJ, Shaw GM, den Heijer M, Finnell RH. Neural tube defects and folate: case far from closed. Nat Rev Neurosci. 2006;7(9):724-731.
26. Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. Arch Dis Child. 1976;51(12):944-950.
27. Smithells R, Sheppard S, Schorah CJ, Seller MJ, Nevin NC, Harris R, et al. Apparent prevention of neural tube defects by periconceptional vitamin supplementation. Arch Dis Child. 1981;56:911-918.
28. Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. BMJ. 1981;282(6275):1509-1511.
29. Kirke PN, Daly LE, Elwood JH. A randomised trial of low dose folic acid to prevent neural tube defects. The Irish Vitamin Study Group. Arch Dis Child. 1992;67:1442-1446.
30. Mulinare J, Cordero J, Erickson JD, Berry R. Periconceptional Use of Multivitamins and the Occurrence of Neural Tube Defects. JAMA. 1988;260(21):3141-3145.
31. MRC Vitamin Study Research Group. Prevention of neural tube defects : Results of the Medical Research Council Vitamin Study. Lancet. 1991;338(8760):131-137.
32. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832-1835.
33. Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrent neural tube defects. JAMA. 1993;269(10):1257-1261.
34. Agarwal SS. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. Indian J Med Res. 2000;122:206-211. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/155/CN-00328155/frame.html.
35. Chen G, Song X, Ji Y, Zhang L, Pei L, Chen J, et al. Prevention of NTDs with periconceptional multivitamin supplementation containing folic acid in China. Birth Defects Res Part A - Clin Mol Teratol. 2008;82(8):592-596.
36. Berry RJ, Zhu L, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural tube defects with folic acid in China. N Engl J Med. 1999;341(20):1485-1490.
37. De-Regil LM, Fernández-Gaxiola AC, Dowswell T, Peña JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2010;2(10):1-135.
38. Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. Cochrane Database Syst Rev. 2001;(3):Art.No.CD001056.

39. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane database Syst Rev. 2015;12(12):CD007950.
40. Daly S, Mills JL, Molloy A, Conley M, Lee YJ, Kirke PN, et al. Minimum effective dose of folic acid for food fortification to prevent neural tube defects. Lancet. 1997;350:1666-1669.
41. CDC (Center for Disease Control). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR. 1992;41(RR-14):1-7.
42. Douglas Wilson R, Audibert F, Brock JA, Carroll J, Cartier L, Gagnon A, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. J Obstet Gynaecol Canada. 2015;37(6):534-549.
43. Czeizel AE. Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities. Birth Defects Res Part A - Clin Mol Teratol. 2009;85(4):260-268.
44. Botto LD, Olney RS, Erickson JD. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. Am J Med Genet C Semin Med Genet. 2004;125C(1):12-21.
45. Bailey LB, Berry RJ. Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. Am J Clin Nutr. 2005;81(5):1213S-1217S.
46. Van Beynum IM, Kapusta L, Bakker MK, Den Heijer M, Blom HJ, De Walle HEK. Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: A registry-based case-control study in the northern Netherlands. Eur Heart J. 2010;31(4):464-471.
47. Kelly D, O'Dowd T, Reulbach U. Use of folic acid supplements and risk of cleft lip and palate in infants: a population-based cohort study. Br J Gen Pract. 2012;62(600):e466-72.
48. Paranjothy S, Broughton H, Evans A, Huddart S, Drayton, M, Jefferson R, et al. The role of maternal nutrition in the aetiology of gastroschisis: An incident case-control study. Int J Epidemiol. 2012;41(4):1141-1152.
49. Mills JL, Carter TC, Kay DM, Browne m, Brody LC, Liu A, et al. Folate and Vitamin B12 Related Genes and Risk for Omphalocele. Hum Genet. 2012;131(5):739-746.