

A fejlődési rendellenességek elsődleges megelőzése

az un. magzatvédő-vitaminokkal

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Összefoglalás

Dr. Czeizel Endre a folsav és folsav-tartalmú multivitamin fejlődési rendellenességeket és koraszületést megelőző hatását igazoló vizsgálatainak eredményeit tekinti át e közlemény három részében. Az első részben a két intervenció: a randomizált kontrollált és kohort kontrollált kutatások eredményeit foglalja össze, amely szerint a 0,8 mg folsavat tartalmazó multivitamin az anencephalia-spina bifida aperta/cystica első előfordulásának 90 %-át volt képes kivédeni. Ezen túl a conotruncalis cardiovascularis malformációk 50 %-át, az obstruktív húgyuti rendellenességek 40 %-át megelőzte, de csökkentette a végtag-hiányos rendellenességek arányát is. A közlemény második részében a folsav és folsav-tartalmú multivitaminok (a szerző ezeket együttesen magzatvédő-vitaminoknak nevezi) alkalmazásának problematikus kérdéseit veszi sorba, mint pl. mi a hatékonyabb a folsav egyedül vagy a folsav-tartalmú multivitamin, mekkora a folsav optimális dózisa, stb.. Végül a harmadik részben a legújabb kutatásaik eredményeit mutatja be. (1) Az ajak- \pm szájpadhasadék és hátsó szájpadhasadék gyakorisága nem csökkent a 0,8 mg folsavat tartalmazó multivitamin kora terhességben történt szedése után. Ezzel szemben a nagy dózisu folsav képes volt e fejlődési rendellenességek mintegy 30 %-át kivédeni. (2) Az antiepileptikumok többsége a humán teratogén gyógyszerek közé tartozik, és ezt elsősorban a vér folát-szintjének csökkenésével magyarázzák. A phenytoin, primidon és carbamazepin teratogenitását a folsav párhuzamos adása jelentős mértékben csökkentette. (3) Ellenőrizték, hogy magzatvédő-vitaminok terhesség alatti szedése növeli-e számottevően az újszülöttek születés súlyát. Kutatásaik eredménye szerint ettől nem kell tartani, de meglepő módon a terhesség harmadik trimeszterében szedett nagyobb dózisu folsav szignifikánsan csökkentette a koraszületés gyakoriságát.

kulcsszavak: terhesség, folsav, folsav tartalmú multivitamin, anencephalia-spina bifida, cardiovascularis malformációk, obstruktív húgyuti rendellenességek, ajak- \pm szájpadhasadék, hátsó szájpadhasadék, antiepileptikumok, koraszületés

Summary

This paper reviews the studies connected with folic acid and folic acid-containing multivitamin in order to prevent neural-tube defects and other congenital abnormalities performed by Dr. Andrew E. Czeizel and his coworkers. The first part of this review summarizes the results of the two Hungarian intervention trials: randomized controlled and cohort controlled trial. A 0.8 mg folic acid containing multivitamin in the periconceptional period was able to prevent about 90% of first occurrence of neural-tube defects, in addition these trials showed first that this multivitamin reduced the incidence of conotruncal cardiovascular malformations by 50 % and of obstructive defects of urinary tract by 40 %, and there was a reduction in congenital limb deficiencies as well. In the second part of this review the problematic questions of periconceptional folic acid and folic acid-containing multivitamin supplementation are discussed, e. g. whether folic acid alone or folic acid containing multivitamin is more effective for the prevention of neural-tube defects and other congenital abnormalities, what is the optimal dose of folic acid, etc. Finally the third part of this review highlighted the results of the recent studies performed by Andrew E Czeizel and his coworkers based on the population-based large Hungarian Case-Control Surveillance of Congenital Abnormalities. (1) The large dose of folic acid reduced the occurrence of two types of isolated orofacial clefts by 30 % though previously the multivitamin containing 0.8 mg folic acid was not able to reduce the incidence of these congenital abnormalities. (2) Most antiepileptic drugs belong to the human teratogenic medicinal products; however, their study showed that the teratogenic effect of phenytoin, primidone and carbamazepine was reduced partially by the concomitant use of folic acid. (3) The high dose of folic acid use in the third trimester of pregnancy reduced significantly the rate of preterm birth.

keywords: pregnancy, folic acid, folic acid-containing multivitamin, neural-tube defects, conotruncal cardiovascular malformations, obstructive defects of urinary tract, orofacial clefts, antiepileptic drugs, preterm birth

Irodalom

1. Smithells RW, Sheppard S, Wild J, Schorah CJ. Prevention of neural tube defect recurrences in Yorkshire: final report. *Lancet* **1989**; 2: 498-499.
2. Tolarova M. Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. *Lancet* **1982**; 2: 217.
3. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* **1991**; 338: 131-137.
4. US National Academy of Sciences. Dietary Reference Intakes: Folate, Other B Vitamins and Choline. National Academy Press. Washington DC, **1988**.
5. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* **1992**; 327: 1832-1835.
6. CDC. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR* **1992**; 41: 1233-1238.
7. Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. *Br Med J* **1993**; 306: 1645-1648.
8. Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* **1996**; 62: 179-183.
9. Czeizel AE: Randomized Controlled Trial of Multivitamin Supplementation on Birth Defects and Pregnancy Outcomes, 1984-1994. Complementary and Alternative Medicine Data Archive, Data Set, Sociometric Corporation, National Institute of Health, 16. October **2004**.
10. Czeizel AE. Ten years of experience in the periconceptional care. *Eur J Obstet Gynecol Reprod Biol* **1999**; 89: 43-49.
11. Czeizel AE, Dobó M, Vargha P. Hungarian cohort controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. *Birth Defects Research, Part A*. **2004**; 70: 853-861.
12. Botto LD, Olney RS, Erickson JD. Vitamin supplements and the risk for congenital anomalies other than neural tube defects *Am J Med Genet Part C* **2004**; 125C: 12-21.
13. Tarusco D (ed.): Folic Acid: From Research to Public Health Practice. *Rapporti ISTISAN 04/26*, Roma. **2004**.
14. Czeizel AE, Merhala Z. Bread fortification with folic acid, vitamin B12 and vitamin B6 in Hungary. *Lancet* **1998**; 352: 1225.
15. Czeizel AE, Kökény M. Flour fortification with folic acid in Hungary. *Br Med J* **2002**; 325: 391.
16. Wicken B, Bamforth F, Li Z, Czeizel AE. Geographical ethnic variation of 677CT allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): findings from over 700 newborns from 16 areas world wide. *J Med Genet* **2003**; 40:619-625.
17. McPartlin J, Halligan A, Scott JM, et al. Accelerated folate breakdown in pregnancy. *Lancet* **1993**; 341: 148-149.
18. Berry RJ, Li Z, Erickson JD et al. Prevention of neural-tube defects with folic acid in China. China-US Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* **1999**; 341: 1485-1490.
19. Czeizel AE, Susánszky E. Diet intake and vitamin supplement use of Hungarian women during preconceptional period. *Int J Vitam Nutr Res* **1994**; 64: 300-305.
20. Erős E, Géher P, Gömör B, Czeizel AE Epileptogenic activity of folic acid after drug induced SLE (folic acid and epilepsy). *Eur J Obstet Gynecol Reprod Biol* **1998**; 80: 75-78
21. Czeizel AE, Intödy Zs, Modell B What proportion of congenital abnormalities can be prevented? *Br Med J* **1993**; 306: 499-503.
22. Czeizel AE. The first 25 years of the Hungarian Congenital Abnormality Registry. *Teratology* 1997; 55: 299-305.
23. Czeizel AE, Rockenbauer M, Siffel Cs, Varga E. Description and mission evaluation of the Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980-1996. *Teratology* **2001**; 63: 176-185.
24. Czeizel AE, Vargha P Periconceptional folic acid/multivitamin supplementation and twin pregnancy. *Am J Obstet Gynecol* **2004**; 191: 790-794.
25. Czeizel AE, Timár L, Sárközi A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. *Pediatrics* **1999**; 104: e66.
26. Czeizel AE. Prevention of oral clefts through the use of folic acid and multivitamin supplements: evidence and gap. In: Wyszynski DF (ed.) *Cleft Lip and Palate. From Origin to Treatment*. Oxford University Press. New York, **2002**. pp. 443-457.
27. Ács N, Bánhidly F, Puho E, Czeizel AE. Maternal influenza during pregnancy and risk of congenital abnormalities on offspring. *Birth Defects Res Part A* 2005; 73: 989-996.
28. Ács N, Bánhidly F, Puho HE, Czeizel AE. Population-based case-control study of the common cold during pregnancy and congenital abnormalities. *Eur J Epidemiol* **2006**; 21: 65-75.
29. Ács N, Bánhidly F, Puho HE, Czeizel AE. Acute respiratory infections during pregnancy and congenital abnormalities: case-control study. *Cong Anom* **2006**; 46: 86-96.
30. Botto LD, Erickson JD, Mulinare J et al. Maternal fever, multivitamin use, and selected birth defects: evidence of interaction? *Epidemiology* **2002**; 13: 485-488.
31. Kjaer D, Horvath-Puho E, Christensen J, Czeizel AE. Antiepileptic drug use, folic acid supplementation, and congenital abnormalities: a population-based case-control study. *Br J Obstet Gynecol* **2008**; 115: 98-103
32. Czeizel AE, Puho HE, Langmar Z et al. Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. *Eur J Obstet Gynecol Reprod Biol* **2010**; 148: 135-140.
33. Cikot RJLM, Steegers-Theunissen RPM, Thomas CMG et al. Longitudinal vitamin and homocysteine levels in normal pregnancy. *Br J Nutr* **2001**; 85: 49-58.
34. van der Molen EF, Verbruggen B, Nokalova I et al. Hyperhomocysteinemia and other thrombotic risk factors in women with placental vasculopathy. *Br J Obstet Gynecol*. **2000**; 107: 785-791.
35. Czeizel AE, Petik D, Puho HE. Smoking and alcohol drinking during pregnancy. The reliability of retrospective maternal self-reported information. *Cent Eur J Publ Health*. **2004**; 12: 179-183.
36. Bukowski R, Malone FD et al. Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study. *PLoS Med* **2009**; 6:e10000061