

Strategies for increasing intake of folic acid Hungarian experience

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Periconceptional Care

- Check-up of reproductive health
- The 3-month preparation for conception
- Better protection of early pregnancy

Composition of Supplements

"Multivitamin (Elevit Pronatal)"	"Placebo-like Trace Elements"	
Vitamins		
A	4000 IU	
B1	1.6 mg	
B2	1.8 mg	
Nicotinamid	19.0 mg	
B6	2.6 mg	
Calcium Panthothenate	10.0 mg	
Biotin	0.2 mg	
B12	4.0 mcg	
C	100.0 mg	7.5 mg
D	500.0 IU	
E	15.0 mg	
<i>Folic Acid</i>	0.8 mg	
Minerals		
Calcium	125.0 mg	
Phosphorus	125.0 mg	
Magnesium	100.0 mg	
Iron	60.0 mg	
Trace Elements		
Copper	1.0 mg	1.0 mg
Manganese	1.0 mg	1.0 mg
Zinc	7.5 mg	7.5 mg

Contract

Roche

Hungarian Periconceptional
Care

maternal
information

Capsule A, B

Side effect

structured
questionnaire

Goals of the Hungarian randomized double-blind controlled trial (RCT)

About 95% of women with NTD offspring have no previous NTD pregnancies.

- Thus the question is whether the periconceptual folic acid-containing multivitamin supplementation can reduce the first **occurrence** of NTD

The pharmacological dose (> 1 mg, e.g., 4 mg) of folic acid cannot be recommended for the population at large or without medical supervision.

- Thus, the question is whether a **physiological** dose (< 1 mg) is effective or not.

Possible **other beneficial or adverse effects** of periconceptual multivitamin supplementation.

Result of the RCT: Reduction of the First Occurrence of NTD

Study groups	Number of informative offspring	Observed NTD		Expected NTD	
		No.	per 1000	No.	per 1000
Multivitamin	2,471	0	0.00	6.9	2.78
Placebo-like trace element	2,391	6*	2.51	6.6	2.78

Relative risk (with 95% confidence interval) = 0.06 (0.00, 0.63)
Fisher test $P_2 = 0.01$

* anencephaly 2, spina bifida aperta 2, anencephaly + spina bifida 2

Other effects

Side effects:

- Constipation 1.8% vs 0.8%
- Diarrhea 1.4% vs 0.4%
- Four women had severe allergic exanthema (among 14,500 women)

Other effects

During the **preconceptional** multivitamin supplementation

- Female cycle more regular
- No difference in sexual activity
- Higher rate of conception (7%)
- Time to achieve pregnancy shorter
- No maternal weight gain

Intention-to-treat analysis of fetal death

Fetal death	Multivitamin (N=2,793)		Placebo-like (N=2,660)	
	No.	%	No.	%
Chemical pregnancy	55	1.0	40	1.5
Ectopic pregnancy	7	0.2	4	0.2
Miscarriage	301	10.8	251	9.4
Stillbirth	11*	0.4	9	0.3
Total	374	13.4	304	11.4

*3 stillbirths occurred in twin pregnancies in which the other twin was liveborn

Miscarriage $\chi^2=2.69$; $p=0.10$

Total $\chi^2=4.82$; $p=0.03$

Other effects

During the **postconceptional** multivitamin supplementation

- Lower rate of morning sickness
 - severe 3.0% vs 6.6%
 - mild 33.3% vs 50.3%
- No difference in maternal weight gain
- Higher rate of twin births (40%)
- Significant reduction in some other CAs beyond NTD

Distribution of singletons, twins and triplet in the Hungarian RCT

Type of birth	Multivitamin No.	Placebo-like No.
Stillbirth		
Singleton	8	9
One of twins	3	0
Livebirth		
Singletons	2,367	2,305
Twins	84	64
One of twins	3	0
Triplet	3	0
Total	2,468	2,378
Multiple birth No.	93	64
%	3.77	2.69
	$\chi^2_1 = 4.48$	$p = 0.03$

Results of further studies

USA (4/5)	30-60% increase after multivitamin		
Sweden (national)	significant increase after folic acid		
Hungary (national) (HCCSCA)	38,151 395 (1.04%) twins		
Unsupplemented	127	0.78%	
Supplemented	before	28	1.52
	after	240	1.20
			1.80 (1.14-2.85) 1.50 (1.15-1.97)
China (public health program)	0.4 mg folic acid in		
242,015 women			
	supplemented	unsupplemented	
multiple pregnancy rate	0.59%	0.65%	
	very low rate of dizygotic twins		
	TT genotype of MTHFR gene is 20%		

Variables of liveborn singletons

Variables	Multivitamin (N=2,367)		Placebo-like (N=2,305)	
	Mean	S.D.	Mean	S.D.
Quantitative				
Birth weight (g)	3,291	488	3,288	478
Gestational age (yr)	39.6	1.7	39.6	1.6
Categorical	No.	%	No.	%
Low birthweight	101	4.3	81	3.5
Preterm birth	178	7.5	166	7.2
Boy	1,181	49.9	1,196	51.9

Postnatal somatic, mental and behavioural development

Variables	8-16 months (N=1600)	2 years (N=336)	6 years (N=289)
Somatic		Body weight Body length Head circumference Chest circumference	
Cognitive		Hungarian Development Test (2 yr) Binet test (6 yr)	
Behavioural		Vineland test	
Health status		Case history General paediatric exam Audiological exam Ophthalmological exam	

Number and rate (per 1000) of different CA-groups in multivitamin and no multivitamin supplemented group

Categories of CAs Group of CAs	Multivitamin (N=2,471)		No multivitamin (N=2,391)		RR (with 95% CI)
	No.	Rate	No.	Rate	
Isolated CAs					
NTD	0	0.0	6	2.51	0.07 (0.04, 0.13)
Orofacial clefts	4	1.62	5	2.09	0.77 (0.22, 2.69)
Cardiovascular CAs	10	4.05	20	8.36	0.42 (0.19, 0.98)
CAs of urinary tract	2	0.81	9	3.76	0.21 (0.05, 0.95)
Limb deficiencies	1	0.40	5	2.09	0.19 (0.03, 1.18)
Cong. pyloric stenosis	2	0.81	8	3.34	0.24 (0.05, 1.14)
Others	22	8.90	32	13.38	0.68 (0.37, 1.10)
Multiple CAs	10	4.05	12	5.02	0.81 (0.36, 1.26)
Total	51	20.64	97	40.57	0.53 (0.35, 0.70)

Reduction of NTD by periconceptional folic acid-containing multivitamin supplementation in two Hungarian intervention studies

Intervention studies	Supplemente d	Unsupplemente d
Randomized controlled trial No. of informative offspring No. of NTD offspring RR (95%CI)	2,471 0 0.06 (0.04,0.13)	2,391 6
Two-cohort controlled study No. of informative offspring No. of NTD offspring OR (95% CI)	3,056 1 0.11 (0.01,0.91)	3,056 9
Together No. of informative offspring No. of NTD offspring OR (95% CI)	5,527 1 0.08 (0.01,0.47)	5,447 15

Number of informative offspring with cardiovascular CAs in multivitamin (MV) and no multivitamin (No-MV) groups

Cardiovascular CAs	RCT		TCS		Pooled data	
	MV (N=2,471) No.	No-MV (N=2,391) No.	MV (N=3,056) No.	No-MV (N=3,056) No.	MV (N=5,527) No.	No-MV (N=5,447) No.
Conotruncal						
Ventricular septal defect	2	8	5	19	7	27
Others	1	2	3	1	4	3
Subtotal	3	10	8	20	11	30
Others	7	10	23	30	30	40
Total	10	20	31	50	41	70
OR (with 95% CI)	0.42 (0.19, 0.98)		0.60 (0.38, 0.96)		0.57 (0.39, 0.85)	

Number of informative offspring with urinary tract's CAs in multivitamin (MV) and no multivitamin (No-MV) groups

CAs of urinary tract	RCT		TCS		Pooled data	
	MV (N=2,471) No.	No-MV (N=2,391) No.	MV (N=3,056) No.	No-MV (N=3,056) No.	MV (N=5,527) No.	No-MV (N=5,447) No.
Renal a/dysgenesis	0	3	2	0	2	3
Cystic kidney	1	1	2	0	3	1
Obstructive CAs						
Pelvicureteric	0	4	2	13	2	17
Others	1	1	8	6	9	7
Subtotal	1	5	10	19	11	24
Total	2	9	14	19	16	28
OR (with 95% CI)	0.21 (0.05, 0.95)		0.71 (0.33, 1.50)		0.50 (0.30, 1.04)	

Number of informative offspring with other „candidate” CAs in multivitamin (MV) and no multivitamin (No-MV) groups

Other „candidate” CAs	RCT		TCS		Pooled data	
	MV (N=2,471) No.	No-MV (N=2,391) No.	MV (N=3,056) No.	No-MV (N=3,056) No.	MV (N=5,527) No.	No-MV (N=5,447) No.
Orofacial clefts						
Cleft lip ± palate	4	3	3	2	7	5
Posterior cleft palate	0	2	1	1	1	3
Total	4	5	4	3	8	8
OR (with 95% CI)	0.77 (0.22, 2.69)		1.63 (0.31, 28.8)		0.99 (0.37, 2.63)	
Limb deficiencies	1	5	1	3	2	8
OR (with 95% CI)	0.19 (0.03, 1.18)		0.33 (0.01, 3.71)		0.25 (0.05, 1.16)	
Cong. pyloric stenosis	2	8	0	2	2	10
OR (with 95% CI)	0.24 (0.05, 1.14)		0.00 (0.00, 26.8)		0.20 (0.04, 0.90)	
Anal/rectal atresia/stenosis	0	1	1	4	1	5
OR (with 95% CI)	—		0.31 (0.02, 2.52)		0.20 (0.02, 1.69)	

Multiple congenital abnormalities

Shaw et al. Am J Med Genet 2000

Periconceptional intake of vitamin supplements and risk of multiple congenital abnormalities

Czeizel-Medveczky. Obstet Gynecol 2003

Periconceptional multivitamin supplementation and multimalformed offspring

Yuskin et al. Am J Med Genet 2005

Reported multivitamin supplementation and the occurrence of multiple congenital anomalies

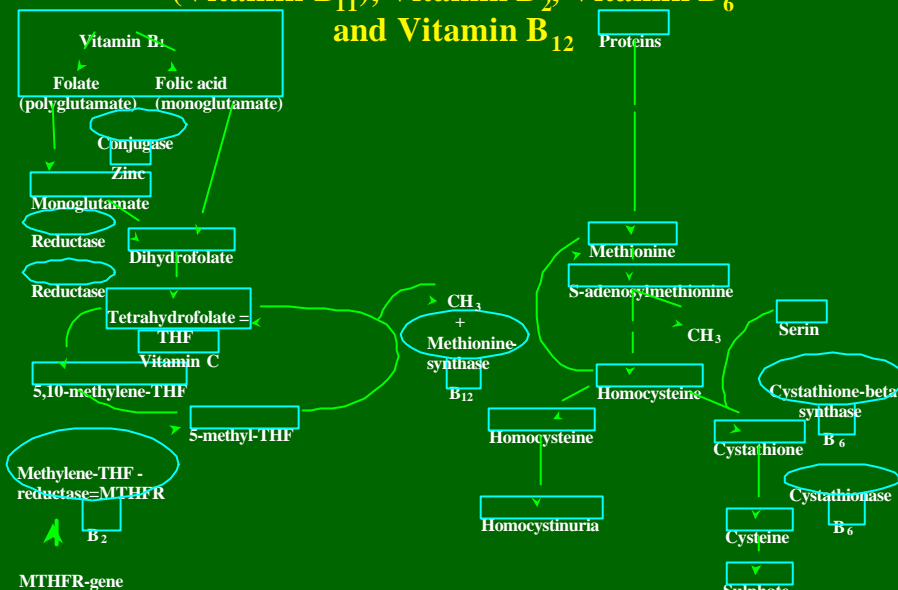
Czeizel et al. Am J Med Genet 2006

No association between periconceptional multivitamin supplementation and risk of multiple congenital abnormalities

Acute toxicity of folic acid in pregnant women

No.	Maternal age (yr)	Gestational age (wk)	Folic acid (mg)	Toxic effect in pregnant women	Exposed child (birth weight + health status)
1.	22	34	120	No	3,090 g Good
2.	17	22	120	No	2,450 g Good (adopted)
3.	17	34	150	No	3,400 g Congenital inguinal hernia
4.	31	18	120	No	1,750 g Good

Metabolism of Homocysteine and the Effect of Folate-Folic Acid (Vitamin B₁₁), Vitamin B₂, Vitamin B₆ and Vitamin B₁₂



MTHFR gene

- Gene location: Chromosome 1, short arm 36.3
- Mutation: 677 T → C
- Frequency of
 - mutant homozygosity: 5-15 % (11%)
 - heterozygosity: 25-65% (45%)

General Prevention

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graph TD; A[General Prevention] --> B["Diet rich in folate and other vitamins"]; A --> C["Periconceptional multivitamin/folic acid supplementation"]; A --> D["Food fortification"];
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Diet rich in folate and other vitamins

Periconceptional multivitamin/folic acid *supplementation*

Food fortification

Difficulties in dietary strategy to increase folate intake

Low mean folate intake 0.18 mg/day

Optimal folate intake 0.66 mg/day

Low bioavailability of folate in food 30-80 %

Natural food folate is relatively ineffective at increasing folate status (aggressive intervention with dietary folate did not increase red-cell folate level).

Difficulties of periconceptional supplementation

Large proportion of pregnancies are unplanned.

Low proportion of planned pregnancies are supplemented.

Theoretical problems (folic acid alone or multivitamins, dose).

Folic acid alone or folic acid-containing multivitamin

Folic acid alone

Multivitamin

Efficacy

70% of NTD

92% of NTD

Other effects

?

Prevention of other major CAs

Theoretical background (in hyperhomocysteinemia related NTD)

Key factor

However, vitamin B12, B2
and B6 are independent factors.

Food fortification

USA
Canada
Chile
Ireland

Hungary

(August 20, 1998)

Microgram

Vitamin

Bread
(200 g)

Folic acid 200

Vitamin B12 1

Vitamin B6 1800

(January 1, 2006)

Flour
(100 g)

Folic acid 350

Vitamin B12 10

Vitamin B6 1600

Vitamin B2 500

Hungarian experiences

Facts

Voluntary fortification

media campaign is expensive
price is higher (antisocial)
consumption is low

Arguments

Mandatory fortification

information for public is enough
not expensive (governmental support)
consumption is high

General conclusion

Inertia on the use of folic acid or folic acid containing multivitamins for the primary prevention of CAs is medical malpractice

