

# **Primary Prevention of Birth Defects by Periconceptional Folic-Acid Containing Multivitamin / Folic-Acid Supplementation**

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# Introduction

Periconceptional folic acid or folic acid-containing multivitamin supplementation has been shown to have a clear preventive effect on the recurrence and first occurrence of neural-tube defects (NTD), therefore this primary preventive method is recommended for prospective pregnant women.

# Composition of Supplements

"Multivitamin in (Elevit Pronatal)"	"Placebo-like Trace Elements"	
<b>Vitamins</b>		
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	
<b>Minerals</b>		
Calcium	125.0 mg	
Phosphorus	125.0 mg	
Magnesium	100.0 mg	
Iron	60.0 mg	
<b>Trace Elements</b>		
Copper	1.0 mg	1.0 mg
Manganese	1.0 mg	1.0 mg
Zinc	7.5 mg	7.5 mg

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

Intervention studies	Supplemented	Unsupplemented
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 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, 0,81)
<b>Total</b>	<b>51</b>	<b>20.64</b>	<b>97</b>	<b>40.57</b>	<b>0.53 (0.35, 0.70)</b>

# Question 1.:

Can folic acid-containing multivitamin prevent other defects beyond neural-tube defects?

# Reply – Probable

Congenital abnormality (CA)	Our cohort controlled trial OR 95% CI	US observational studies Yes / No
Cardiovascular CA	0.60, 0.38-0.96	-
Conotruncal CA	0.26, 0.09-0.72	3 / 1
CA of urinary tract	0.74, 0.34-1.55	2 / 0
Obstructive CA of pelvic - ureteric junction	0.15, 0.02-0.68	-
Limb deficiencies (/terminal transverse)	0.25, 0.05-0.16	3 / 0
	-	

# WHO Expert Committee (2004)

Folic acid-containing multivitamins  
can reduce the incidence of  
congenital defects by about one third

## Question 2.:

What is the mechanism of folic acid or folic acid-containing multivitamins in the prevention of NTD and other CA?

# Reply

These CAs are caused by

polygenic — environmental interaction

different gene mutations, e.g. hyperhomocysteinemia	different factors, mainly dietary vitamin (folate) deficiency
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## Question 3.:

Is dietary strategy to increase folate intake can neutralise the genetic predisposition for these CAs?

**Reply:** unlikely

# Why?

Low mean folate intake	0.18 mg/day
Optimal dose for prevention of NTD (McPartlin et al., 1993)	0.66 mg/day
Difference (15 plates of spinach or broccoli!)	0.50 mg/day
Low bioavailability of folate in food (30-80%)	
There is a threshold in folate absorption from gastroenteral system	

Periconceptional folic acid or folic acid-containing supplementation seems to be appropriate

However,

## **Question 4.:**

Whether folic acid alone or folic acid-containing multivitamin is better?

# Folic acid alone or folic acid-containing multivitamin

## Folic acid alone

## Multivitamin

### Efficacy

70% of NTD

90% of NTD

### Other effects

?

Prevention of other major CAs

### Other arguments in hyperhomocysteinemia related NTD

Key factor

Vitamin B12, B2 and B6 are independent factors

### Cost

Low

Moderate (reimbursement)

# Question 5.:

Which multivitamin is recommended?  
There is only one product (Elevit®) that  
was tested in RCT

## Question 6.:

**What is the optimal dose of folic acid?**

No scientific evidence

There are two forms of Vitamin 11 (or 9)

dietary polyglutamate folate

synthetic monoglutamate folic acid

US recommendation

0.4 mg (400 microgram) folic acid

The Institute of Medicine, US National  
Academy (1998) –

European Commission Scientific Committee on  
Food (1998)

**physiological dose** of folic acid (less than 1 mg)  
for preventive purpose in healthy people

**pharmacological dose** of folic acid (more than  
1 mg) for treatment of patients or under permanent  
medical control

# Pros and cons

Wald et al (2001): dose/effect relation for folic acid in the reduction of hyperhomocysteinemia and related NTD

Daily et al (1997): there is no obvious increase in the reduction of NTD due to higher doses of folic acid

## Reasonable recommendation:

Folate	0.2 – 0.3 mg
<u>Folic acid</u>	<u>0.7 – 0.8 mg</u>
Together	1.0 mg

# General conclusion

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

