The Folic Acid Rescue Strategy: High Dose Folic Acid Supplementation in Early Pregnancy

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University of Toronto, Canada

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NEURAL TUBE DEFECTS

• An estimated > 300,000 worldwide / year
• The consequences: mortality, morbidity, disabilities and huge economic burden.
• In 2008 the total lifetime direct cost for Spina Bifida in US $706,000.
• About 50-70% of NTDs could be prevented by adequate folic acid supply in the critical period of organogenesis.
• In reality, this huge potential is vastly underutilized, despite very specific public health recommendations issued by health organizations worldwide.
NEURAL TUBE DEFECTS
CRITICAL TIME OF ORGANOGENESIS

<table>
<thead>
<tr>
<th>Main Embryonic Period (in weeks)</th>
<th>Fetal Period (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
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</tbody>
</table>

### Neural tube defects (NTDs)
- TA, ASD, and VSD
  - Heart
- Amelia/Meromelia
  - Upper limb
- Amelia/Meromelia
  - Lower limb
- Cleft lip
  - Upper lip
- Low-set malformed ears and deafness
- Eyes
- Ears
- Microphthalmia, cataracts, glaucoma

### Mental retardation

### CNS

<table>
<thead>
<tr>
<th>Common site(s) of action of teratogens</th>
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<tbody>
<tr>
<td>Less sensitive period</td>
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<tr>
<td>Highly sensitive period</td>
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<table>
<thead>
<tr>
<th>Major congenital anomalies</th>
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<tr>
<td>Functional defects and minor anomalies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TA — Truncus arteriosus; ASD — Atrial septal defect; VSD — Ventricular septal defect</th>
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Death of embryo and spontaneous abortion common.
EVIDENCE FOR THE EFFICACY OF
PERICONCEPTIONAL FOLIC ACID
SUPPLEMENTS IN THE PREVENTION OF CM

<table>
<thead>
<tr>
<th>TYPE OF CM</th>
<th>STUDY (PUBLICATION)</th>
<th>ODDS RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTD</td>
<td>CHINA (N=130,000) (NEJM, 1999)</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>NTD</td>
<td>ATLANTA, USA (JAMA, 1988)</td>
<td>0.4</td>
</tr>
<tr>
<td>CHD*</td>
<td>ATLANTA, USA (PEDIATRICS, 1996)</td>
<td>0.57</td>
</tr>
<tr>
<td>CHD</td>
<td>BUDAPEST (COMMUN GENET, 1998)</td>
<td>0.42</td>
</tr>
<tr>
<td>GENITO-URINARY**</td>
<td>BOSTON, USA (AM J EPID, 1999)</td>
<td>0.5</td>
</tr>
<tr>
<td>GENITO-URINARY</td>
<td>WA, USA (EPIDEMIOLOGY, 1995)</td>
<td>0.5</td>
</tr>
<tr>
<td>CLEFT LIP / PALATE</td>
<td>CALIFORNIA, USA (LANCET, 1995)</td>
<td>0.6</td>
</tr>
<tr>
<td>LIMB REDUCTION</td>
<td>BOSTON, USA (AM J EPID, 1999)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* INCLUDING: CONOTRUNCAL DEFECTS: TGA, TOF, VSD
** INCLUDING: RENAL AGENESIS, URINARY TRACT OBSTRUCTION
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 between the 21st-26th postconception day in the cranial pole and between the 23rd-28th day in the caudal pole, respectively.

However, in clinical practice the so-called gestational age is calculated from the 1st day of the last menstrual period. Therefore, in women with normal 28 days of period it is necessary to add 14 days to the postconception age to calculate the gestational age.

Thus the critical period for anencephaly is the 35th - 40th gestational day, while the critical period for spina bifida is 37th - 42nd gestational days (i.e. gestational week 5-6)
Time of initiation of folic acid supplementation in Spain, BMJ, November 2015

Use of high doses of folic acid supplements in pregnant women in Spain: an INMA cohort study

Eva María Navarrete-Muñoz,1,2 Desirée Valera-Gran,1 Manoli García de la Hera,1,2

Figure 1  Folic acid supplements use among 2422 participants in all cohorts of the INMA Project, Spain (2003-2008). Percentage by months of pregnancy.
**Table 3. Rates of Neural-Tube Defects According to the Pattern of Use of Folic Acid Pills.**

<table>
<thead>
<tr>
<th>Pattern of Use*</th>
<th>Pregnant Women†</th>
<th>Mean Compliance</th>
<th>Neural-Tube Defects Rate/1000 Pregnancies of ≥20 wk No. Gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periconceptional use</td>
<td>13,012 (70)</td>
<td>81</td>
<td>13</td>
</tr>
<tr>
<td>Late use</td>
<td>3,681 (20)</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>1,838 (10)</td>
<td>68</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>18,531 (100)</td>
<td>78</td>
<td>25</td>
</tr>
<tr>
<td>Southern region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periconceptional use</td>
<td>58,638 (53)</td>
<td>87</td>
<td>34</td>
</tr>
<tr>
<td>Late use</td>
<td>35,647 (32)</td>
<td>74</td>
<td>25</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>17,107 (15)</td>
<td>78</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>111,392 (100)</td>
<td>81</td>
<td>77</td>
</tr>
</tbody>
</table>

*We defined women with periconceptional use as those who started taking folic acid pills before their last menstrual period before conception and who stopped at the end of the first trimester. We defined women with late use as those who started taking folic acid pills during the first trimester but sometime after their last menstrual period. We defined women with early discontinuation of folic acid pills as those who started and stopped taking folic acid pills before their last menstrual period before conception.
Preventing Neural Tube Birth Defects:

A Prevention Model and Resource Guide

**REPRODUCTIVE TIME LINE**

9 Months

1st Trimester  2nd Trimester  3rd Trimester

Conception  Recognition of Pregnancy  Birth

Neural Tube Development

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First printing – November 1998
Second printing – March 1999
Third printing – October 2000
Fourth printing – January 2002
Fifth printing – December 2004
Sixth printing – April 2009

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About Folic Acid

When Do Women Need to Take Folic Acid?............
How Much Folic Acid Is Needed to Prevent NTDs?....
Are Women Getting Enough Folic Acid?..............
How Can Women Get Enough Folic Acid?.............
METHODS FOR INCREASING FOLIC ACID INTAKE
THE TRIPLE STRATEGY

• **DIETARY INTAKE** (LEAFY GREEN VEGETABLES, YEAST, CITRUS, LIVER, KIDNEY)

• **LIMITATIONS**: LENGTHY COOKING DESTROYS FA,

• **FOOD FORTIFICATION**: IN FLOUR, CEREALS, ETC.

• **SUPPLEMENTATION**: DAILY PILLS- 0.4 mg
  
  (5 mg per day to prevent recurrent NTD)
Public health officials have considered 3 approaches to achieving the CDC recommendation for a daily folic acid intake of 0.40 mg: (1) promoting daily use of folic acid–containing vitamin supplements, (2) promoting dietary intake of folate-rich foods, and (3) fortifying food with folic acid. The US Approaches 1 and 2

The prevalence of daily folic acid supplementation during the periconceptional period was 29% overall, changing from 25% in 1993 to 30% in 1994 and to 34% in 1995.
FIGURE. Prevalence of neural tube defects (NTDs) (anencephaly and spina bifida) before and after mandatory folic acid fortification, by maternal race/ethnicity — 19 population-based birth defects surveillance programs,* United States, 1995–2011
GAP BETWEEN PREDICTION AND REALITY

In 1995, Daly et al. predicted that the recommendation to increase folic acid intake of 0.4 mg per day would result in a 48% reduction in NTDs.

- A report from the USA (2015), using a large scale population-based data showed that subsequent to food fortification there was only a 35% reduction in the prevalence of NTDs.

- This reduction was observed in the immediate period after initiation of food fortification, but has leveled off during the following ten years.

- Since the recommendation for folic acid supplementation to all women in the child-bearing age has been implemented in the USA in parallel to food fortification, the decrease in the occurrence of NTDs is attributed to the combined effect of food fortification and daily supplementation.
FAILURE OF THE STRATEGY OF PRE-CONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR PREVENTION OF NTSs IN EUROPE:

1. LOW INTAKE (low compliance and adherence)
2. NTDs rates has not dropped in 20 years!!!

Based on BMJ November 2015

Long term trends in prevalence of neural tube defects in Europe: population based study

Babak Khoshnood,1 Maria Loane,2 Hermien de Walle,3 Larraitz Arriola,4 Marie-Claude Addor,5

METHODS
This was a population based, observational study using data on 11353 cases of NTD not associated with chromosomal anomalies, including 4162 cases of anencephaly and 5776 cases of spina bifida from 28 EUROCAT (European Surveillance of Congenital Anomalies) registries covering approximately 12.5 million births in 19 countries between 1991 and 2011.

SUMMARY ANSWER AND LIMITATIONS
Overall, the pooled total prevalence of NTD during the study period was 9.1 per 10 000 births. Prevalence of NTD fluctuated slightly but without an obvious downward trend, with the final estimate of the pooled total prevalence of NTD in 2011 similar to that in 1991.
INCREASE IN PRECONCEPTIONAL FOLIC ACID SUPPLEMENTATION IN ISRAEL

periconceptional folic acid intake %

- 5 (2000)
- 31 (2002)
- 34 (2005)
- 58 (2010)
LOW COMPLIANCE & LOW ADHERENCE

What is Medication Adherence?

- **Medication Adherence**: The patient’s conformance with the provider’s recommendation with respect to **timing**, **dosage**, and **frequency** of medication-taking during the prescribed length of time

- **Compliance**: Patient’s passive following of provider’s orders

- **Persistence**: Duration of time patient takes medication, from initiation to discontinuation of therapy
ADHERENCE (%) TO PRECONCEPTIONAL FOLIC ACID SURVEY IN 225 POSTPARTUM WOMEN, JERUSALEM, 2013-2015

[Diagram showing adherence rates for different groups and days of intake.]
Drugs don’t work in patients who don’t take them.

— C. Everett Koop, M.D.

The average rates of adherence in clinical trials can be remarkably high, owing to the attention study patients receive and to selection of the patients, yet even clinical trials report average adherence rates of only 43 to 78 percent among patients receiving treatment for chronic conditions.\textsuperscript{3,6,7} There is no consensual standard for what constitution.\textsuperscript{12,78-80} Successful methods are complex and labor intensive, and innovative strategies will need to be developed that are practical for routine clinical use.\textsuperscript{12} Given the many factors contributing to poor adherence to medication, a multifactorial approach is required, since a single approach will not be effective for all patients.\textsuperscript{81,82} Table 3 lists some
ADHERENCE WITH MEDICATIONS

Nearly 3 out of 4 Americans admit that they do not always take their medication as directed.

This problem causes... 1/3 of medicine-related hospitalizations.

Nearly 125,000 deaths in the U.S. each year.

Number of Americans affected by a chronic condition requiring medication therapy is expected to grow from 133 million to 157 million by 2020.

Almost $300 billion in avoidable costs to the healthcare system annually.

Source: www.scriptyourfuture.org
STAGES OF REDUCED ADHERENCE

- Rx Prescribed: 100%
- Rx Filled: 88%
- Rx Taken: 76%
- Rx Continued: 47%

Reduction by 12% at each stage.
Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform

David M. Cutler, Ph.D., and Wendy Everett, Sc.D.

study showed that even among patients who have health plans with no cost sharing for medications, rates of nonadherence were nearly 40\%.

The bottom line is this: We’ve known for some time that improved adherence can lead to improvements in health outcomes and reductions in health care spending. What we haven’t known is where to start. With the new
DOSE EFFECT RELATIONSHIP: FOLIC ACID FOR NTDs PREVENTION
A THRESHOLD OF 906 nmol/L in RBC

Daly et al
JAMA 1995
EWING, N.J., March 4, 2014

First Response™ Reaches Another Milestone with Enhanced Pregnancy Test Technology

FDA Clears Only At-Home Tests to Tell a Woman if she is Pregnant 6 Days Before her Missed Period and with 99% Accuracy from the Day of Expected Period
Most women (94%) had realised they were pregnant by six weeks’ gestation and for three out of four women (76%) their pregnancy was planned.

Almost all women (96%) had contacted a health professional about their pregnancy by the time they were 12 weeks pregnant and 91% had attended a booking appointment.

Almost all women recognised very early on that they were pregnant and a home pregnancy test confirmed this for 94% of women. Very few had their pregnancy confirmed by a midwife (3.3%) and slightly more women who had not previously given birth saw a doctor for confirmation (15% compared with 11%).
Almost all women recognised very early on that they were pregnant and a home pregnancy test confirmed this for 94% of women. Very few had their pregnancy confirmed by a midwife (3.3%) and slightly more women who had not previously given birth saw a doctor for confirmation (15% compared with 11%).

### Table 1. Mean number of weeks’ gestation when women first realised they were pregnant

<table>
<thead>
<tr>
<th>Number of weeks (n)</th>
<th>Mean</th>
<th>S.D.</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primiparous (2,192)</td>
<td>5.1</td>
<td>3.9</td>
<td>4</td>
<td>1-41</td>
</tr>
<tr>
<td>Multiparous (2,196)</td>
<td>5.2</td>
<td>3.5</td>
<td>4</td>
<td>1-42</td>
</tr>
<tr>
<td>All women (4,525)</td>
<td>5.2</td>
<td>3.8</td>
<td>4</td>
<td>1-42</td>
</tr>
</tbody>
</table>
Table 3. Number of weeks pregnant when first saw a health professional about care

<table>
<thead>
<tr>
<th>Number of weeks (n)</th>
<th>Mean</th>
<th>95% confidence interval</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primiparous women (2,172)</td>
<td>7.1</td>
<td>7.0, 7.2</td>
<td>7</td>
<td>0, 40</td>
</tr>
<tr>
<td>Multiparous women (2,179)</td>
<td>7.8</td>
<td>7.6, 7.9</td>
<td>8</td>
<td>0, 36</td>
</tr>
<tr>
<td>All women (4,489)</td>
<td>7.5</td>
<td>7.4, 7.6</td>
<td>8</td>
<td>0, 39</td>
</tr>
</tbody>
</table>
The Last Call Strategy: High Dose Folic Acid Supplementation in Early Pregnancy

- Many women do not take regular periconceptional folic acid (unplanned pregnancies, low compliance and adherence)
- Recommendation to take daily folic acid supplementation during child-bearing age is hard to keep
- The window of opportunity to elevate folic acid at the critical time is narrow
- A China-US study has shown that the risk of NTDs among offspring of women who started 0.4 mg folic acid, with about 75% compliance, only upon recognizing they have conceived was significantly lower than among those with no periconceptional supplementation.
- High dose folic acid (5mg) has shown to confer more rapid and higher peak level of folic acid than upon receiving 1.1mg.
- As more women use home kits for early detection of pregnancy, the number of women who can benefit from the “Last Call strategy” is increasing.
- Implementation of this concept will necessitate linking early detection of pregnancy with immediate initiation of high dose folic acid supplementation.
The Folic Acid Rescue Strategy
High-Dose Folic Acid Supplementation in Early Pregnancy

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Neural tube defects (NTDs) are serious birth defects with more than 300,000 deliveries annually worldwide, causing increased mortality, morbidity, disabilities, and economic burden. About 50% to 72% of NTDs are preventable by adequate folic acid supply in the critical period of organogenesis.1,2 This potential is vastly underused despite extensive public health efforts. The policy of folic acid supplementation is falling and has led to health inequalities.3 We analyze the current state of preconceptional folic acid use and propose the Folic Acid Rescue Strategy to increase the potential of folic acid supplementation in NTD prevention.

Critical Timing of NTD Closure
The brain and spinal cord develop from the neural tube by dorsal folding of the neural plate after the 15th postconception day. The fusion of this folding is completed between the 21st and 26th postconception day in the cranial pole and between the 23rd and 28th day in the caudal pole, respectively. However, in clinical practice the so-called gestational age is calculated from the first day of the last menstrual period. Therefore, in women with a normal 28-day period cycle, 14 days should be added to the postconception age to calculate gestational age. Thus,

Failure of the Strategy of NTD Prevention
Following the US Food and Drug Administration recommendation of folic acid intake, 0.4 mg/d, for all women of childbearing age by improving dietary habits, food fortification, and dietary supplements, US NTD rates decreased from 10.7 in 10,000 to 7.0 in 10,000 in 2009 to 2011.4 However, in Europe, where many countries do
PREVENTION OF CONGENITAL HEART DEFECTS BY 5 Mg FOLIC ACID/DAY

Folic acid in pregnant women associated with reduced prevalence of severe congenital heart defects in their children: a national population-based case–control study

Andrew E. Czeizel a,*, Attila Vereczkey b, István Szabó c


Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

Study design: Evaluation of medically recorded use of folic acid (calculated daily average 5.6 mg) during the critical period of development of eight types of CHD (verified through autopsy reports or after catheter examination and/or surgical correction) in the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA), 1980–1996, containing 22,843 cases with congenital abnormalities and 38,151 population controls without any CHDs, including 5395 matched controls of 3567 live-born cases with various CHDs. A conditional logistic regression model was used to

Results: There was a significant decrease in the prevalence of cases with ventricular septal defect (OR 0.57, 95% CI 0.45–0.73), tetralogy of Fallot (OR 0.53, 95% CI 0.17–0.94), d-transposition of great arteries (OR 0.47, 95% CI 0.26–0.86) and atrial septal defect secundum (OR 0.63, 95% CI 0.40–0.98) in infants born
HOME KITS FOR DETECTING PREGNANCY IN AN ISRAELI PHARMACY - NOVEMBER 2015
Last Call: Fly with folic for a better pregnancy