Women's Health Grand Rounds

November 13, 2003

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Folic Acid Update for Pharmacists

Thomas Lombardi, Pharm.D., FASHP
Clinical Pharmacy Coordinator
St. Peter's Hospital
and
Clinical Associate Professor
Albany College of Pharmacy Albany, NY

Moderator: Mary Applegate, MD, MPH

Viewer Call-In

Phone: 800-452-0662

Fax: 518-426-0696

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Risk of Congenital Anomaly

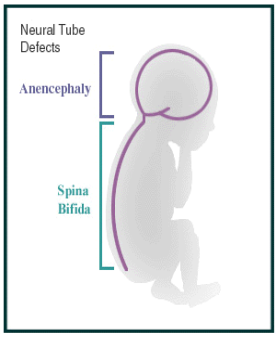
- Congenital malformations are detectable at birth in 3-5% of live births in industrialized nations
- Incidence increases to 8-9% upon following children from birth

Risk of Congenital Anomaly

- Risk factors
  - obstetric and family history
  - consanguinity
  - origin among certain ethnic or national groups
  - maternal age
  - environmental exposures

Neural Tube Defect (NTD)

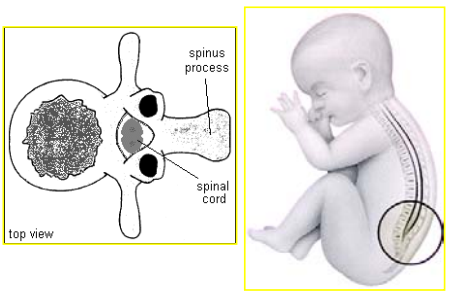
- Defect of the central nervous system
- Includes defects in the spinal cord and brain
- Spina Bifida
  - Latin term meaning "open spine"
  - Medically refers to the birth defect where the spine does not form completely
- Anencephaly
  - Much of the brain, head and possibly the spinal cord do not develop



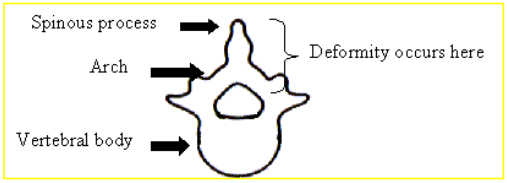
Fetal Stages of Formation of the Central Nervous System

Time	Developmental Event
-2 weeks	Last Menstrual Period (LMP)
0	Fertilization
1 week	Implantation
2 weeks	Formation of the primitive streak and notochord
18 days	Formation of the neural plate
23 days	Formation of the rostral and caudal neuropores
25 days	Closure of the rostral neuropore
27 days	Closure of the caudal neuropore; formation of the blood supply for the neural tube
4th week	Formation of the three primary brain vesicles
5th Week	Beginning of formation of the embryonic cerebrospinal fluid; division of the primary brain vesicles into five secondary brain vesicles

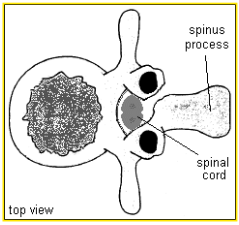
Normal Spine



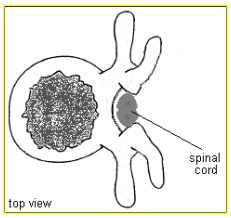
Spina Bifida

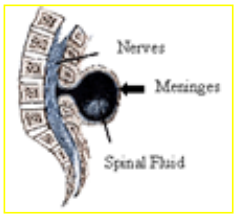


Spina Bifida Oculta



Meningocele

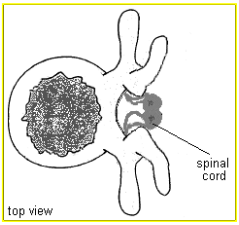


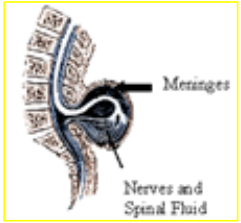


Meningocele

Preparing for Surgery on a Meningocele

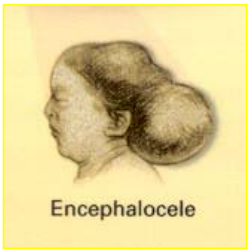
Myelomeningocele





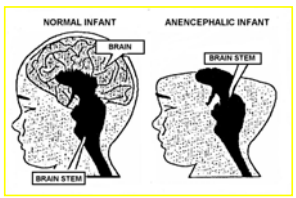
Myelomeningocele

Encephalocele

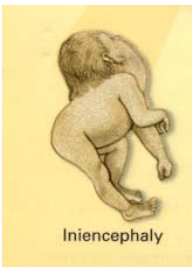


Encephalocele

Anencephaly



Other Neural Tubes Defects



Prognosis & Complications

- Anencephaly, Craniorachischisis, Iniencephaly
  - Incompatible with life
- Encephalocele
  - Can be compatible with life
  - May or may not have long-term disability

Prognosis & Complications

- Spina Bifida
  - Dependent upon the level of involvement
  - Intellectual outcome dependent on complications associated with hydrocephalus
  - Life-Time Cost - estimated at $250,000-$1,000,000
- Family Concerns

Potential Complications

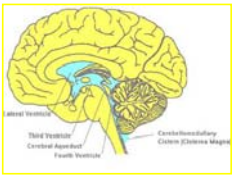
- Limited use of the lower limbs
- Decreased movement and lack of sensation to pain, touch and temperature in areas below the level of the meningomyelocele
- Bowel, kidney and bladder control problems and infection

Potential Complications

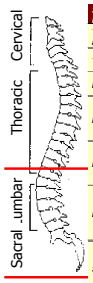
- Foot and leg deformities
- Scoliosis
- Infectious complications associated with bladder, bowel, and chest complications
- Average mental capacity- dependent on hydrocephalus complications

Potential Complications

Hydrocephalus (up to 95%)

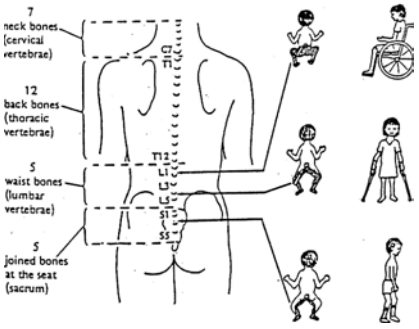


Level of Involvement



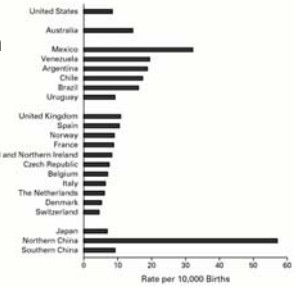
Spinal Level	Reflex	Sensory	Motor
T10 & above			Abdominals (trunk control)
T12			Psoas (hip flexion)
L2		Upper Anterior Thigh	Psoas (hip flexion)
L3		Lower Anterior Thigh Anterior Knee	Psoas (hip flexion) Quadriceps (knee extension) Thigh Adduction
L4	Quadriceps (knee)	Medial Calf	Quadriceps (knee extension) Thigh Adduction Tibialis Anterior (foot dorsiflexion)
L5		Dorsal Surface Foot Lateral Calf	Peronei (foot eversion) Tibialis Anterior (foot dorsiflexion) Gluteus Medias (hip abduction) Toe dorsiflexors
S1	Gastrocnemius/ Soleus (ankle)	Plantar Surface Foot Lateral Aspect Foot	Gastrocnemius/Soleus (foot plantar flexion) Abductor hallicus (toe flexors) Gluteus maximus (hip extension)
S2 & below			Bladder & Bowel Sexual Function

Level of Involvement

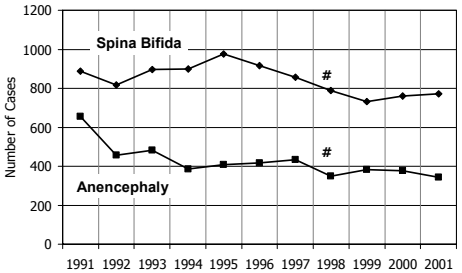


Incidence of NTD

- 400,000 born worldwide each year with a neural tube defect
- Varies among and within countries
- Varies among ethnic groups

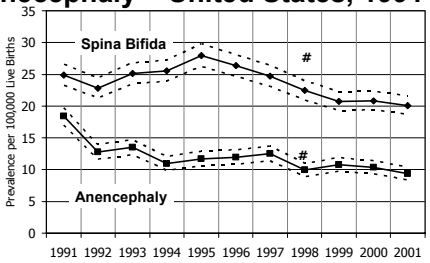


Number of Cases of Spina Bifida and Anecephaly – United States, 1991-2001 *



* Excludes data for Maryland, New Mexico and New York
\# FDA Requires fortification of cereal grains

Prevalence of Spina Bifida and Anecephaly – United States, 1991-2001



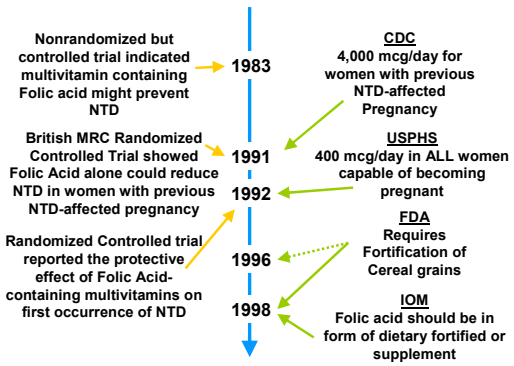
* Excludes data for Maryland, New Mexico and New York
\# FDA Requires fortification of cereal grains

Incidence of NTD

- 90 – 95% of babies born to women with no history of NTD
- 5 – 10% born to women with risk factors
  - women already given birth to a child with a neural tube defect
  - one or both parents have a neural tube defect
  - women with a maternal or paternal history of neural tube defects

Incidence of NTD

- Other Risk Factors
  - Maternal insulin-dependent diabetes
  - Anti-seizure medication (Valproic Acid/Carbamazepine)
  - Medically diagnosed obesity
  - High temperature in early pregnancy
  - Race/Ethnicity (white > black) (Hispanic > non-Hispanic)
  - Lower socio-economic class



Folic Acid

- Pteroylmonoglutamic acid
- Folic acid is an essential vitamin
  - Folic acid is the synthetic form
  - Folate is the natural product
- Required for nucleoprotein synthesis and maintenance of normal erthyropoiesis.
- Stimulates production of red and white cells and platelets in certain megaloblastic anemias.

Folic Acid

- Folic acid is the precursor to tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids
- Impairment of the thymidylate synthesis in patients with folic acid deficiency is believed to cause the defective DNA synthesis that leads to megablast formation and megaloblastic and macrocytic anemias.

Availability of Folic Acid

- Natural Folate is widely distributed in foods
  - Liver
  - Yeast
  - Leafy green vegetables
  - Fruits
  - Nuts
- Heat degrades folate
- Fortified cereal grains (FDA mandated since 1998)
- Supplements

RDA for Folic Acid

RDA Expressed in micrograms of Dietary Folate Equivalents

	Men	Women	Pregnancy	Lactation
Ages 19+	400 mcg	400 mcg		
All ages			600 mcg	500 mcg

1 mcg of food folate = 0.6 mcg folic acid from supplements and fortified food

Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin,riboflavin, niacin, vitamin B6, folate, vitamin B12, panthothenic acid, biotin, and choline. National Academy Press. Washington, DC, 1998.

Trials of Folic Acid to Reduce NTD Among Women With Previous Affected Pregnancy

Investigator (Country)	Folic Acid Dose	Study Design	Results NTD	N	Treatment	Sig
Laurence, et al (Wales)	4 mg	Randomized Compliers vs. Noncompliers	2	60	Folic Acid	NS
			4	51	Placebo	S
Smithells, et al (England)	0.36 mg	Folic Acid as part of a multivitamin	3	454	Folic Acid	SS
			24	519	Placebo	
Vergel, et al (Cuba)	5 mg	Randomized, Placebo Controlled	0	81	Folic Acid	NS
			4	114	Placebo	S
British MRC (England, Hungary)	4 mg	Randomized, Placebo Controlled	6	593	Folic Acid	SS
			21	602	Placebo	

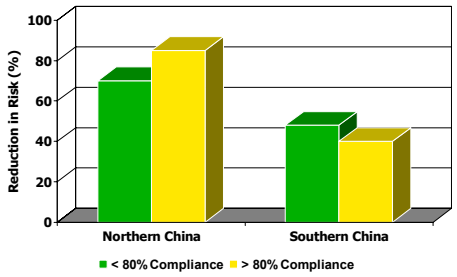
Trials of Folic Acid For Primary Prevention

Investigator (Country)	Folic Acid Dose	Study Design	Results NTD	Treatment	Sig
Mullinare, et al (Georgia, U.S.)	0.4 mg	Case-Control	24	Folic Acid	60% risk reduction
			157	No Supplement	
Bower & Stanley (Australia)	0.4 mg	Case-Control	77	Folic Acid	75% risk reduction
			154	Control	
Mills, et al. (California & Illinois, U.S.)	0.4 mg	Case-Control	89	Folic Acid	No Protective Effect
			214	No Supplement	
Milunsky, et al (New England, U.S.)	0.4 mg	Prospective Cohort	10	Folic Acid	72% risk reduction
			39	No Supplement	
			6	Control	

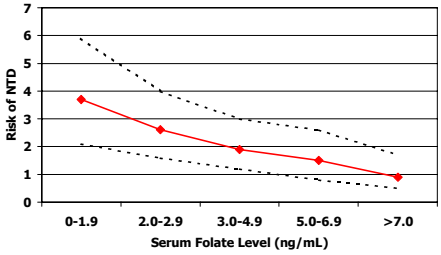
Trials of Folic Acid For Primary Prevention

Investigator (Country)	Folic Acid Dose	Study Design		Results NTD	Treatment	Sig
Werler, et al (Boston, Philidelphia, U.S., Toronto, Canada)	0.4 mg	Case-Control		436	Folic Acid	60% risk reduction
				2615	No Supplement	
Czeizel & Dudek (Hungary)	0.4 mg	Randomized Control		0	Multivitamins	p<0.029
				6	Control	
Berry, et al (China)	0.4 mg	Public Health Registry	North	25	Folic Acid	79% risk reduction
				87	No Supplement	
			South	77	Folic Acid	16% risk reduction
				86	No Supplement	

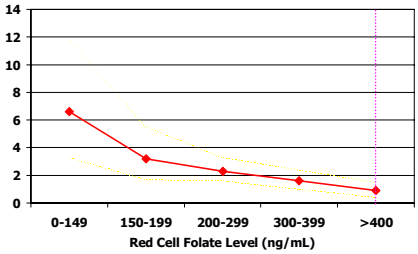
Peri-Conceptional Use of Folic Acid



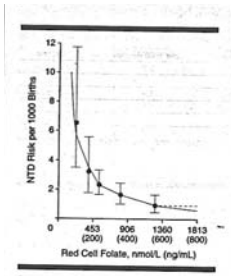
Risk of NTD by Plasma Folate Level



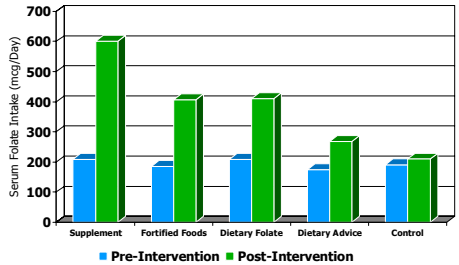
Risk of NTD by Red Cell Folate Level



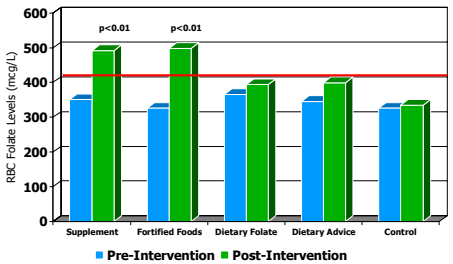
Relationship between Red Cell Folate Levels to Neural Tube Defects



Daily Folate Intake Pre- & Post-Intervention



RBC Folate Levels Pre- & Post-Intervention



Risks of Folic Acid Administration

- Little evidence of acute or chronic toxicity for doses up to 10 mg per day
- Reports of mental status changes with 15 mg per day for 1 month
  - Sleep distrubances
  - Malaise
  - Irritability
  - Excitability
  - Overactivity
- Very high doses may precipitate in the kidneys (animal data)

Risks of Folic Acid Administration

- Very high doses (100 x RDA) can inhibit the uptake of phenytoin
- Reports of GI effects with 5 mg
  - Nausea
  - Abdominal extension
  - Flatulence
  - Bitter Taste
- May mask Pernicious Anemia (Vitamin B12 deficiency)
- Patients should NOT increase folate intake by increasing number of multiple vitamin intake

Folic Acid Recommendations for prevention of Neural Tube Defects (NTD's)

- U.S. Public Health Service
  - Women who could become pregnant should take 400 mcg of folic acid through a vitamin.
  - Women at increased risk for spina bifida should take 4,000 mcg (4 mg) of folic acid for 1 to 3 months prior to pregnancy and should continue through the first trimester.

Folic Acid Recommendations for prevention of NTD's

- CDC
  - Women at increased risk for spina bifida should take 4,000 mcg (4 mg) of folic acid for 1 to 3 months prior to pregnancy and should continue through the first trimester.
- FDA
  - No NDA has been approved by FDA for folic acid for prevention of neural tube defects

Folic Acid Recommendations for prevention of NTD's

- American Academy of Pediatrics
- Women with no history of Previous NTD Affected Pregnancy
- Women who could become pregnant
- 400 mcg folic acid per day through a vitamin.

Folic Acid Recommendations for prevention of NTD's

Women with history of Previous NTD Affected Pregnancy

- During times when pregnancy is not planned
- 400 mcg folic acid per day through a vitamin
- During times when pregnancy is planned
  - 4,000 mcg (4 mg) folic acid per day starting 1 month prior to planned pregnancy throughout the first 3 months of pregnancy, unless contraindicated

Recommendations for use of Folic Acid for prevention of NTD's

Other High Risk Persons are Women with:

- Close relative (sibling, niece, nephew, etc.) with NTD
- Type 1 Diabetes
- Seizure disorder being treated with Valproic Acid or Carbamazepine
- With NTD or Partner with NTD
- Discuss advantages versus disadvantages regarding use of 4,000 mcg (4 mg) folic acid per day with their health care provider

Other Birth Defects That Can Be Prevented With Folic Acid

- Imperforate Anus
- Inconclusive evidence
  - Cardiovascular defects
  - Orofacial clefts
  - Urinary tract defects
  - Limb-reduction defects

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