Webinar

Folic Acid: The Best Tool to Prevent Neural Tube Defects

September 14, 2022

Division of Birth Defects and Infant Disorders
National Center on Birth Defects and Developmental Disabilities

Agenda

- **Introductions**
  - Moderated by CAPT Amanda Cohn, MD |3:00 p.m.
- **Opening Remarks**
  - Karen Remley, MD, MBA, MPH, FAAP | 3:05 p.m.
- **What We Have Learned from 30 Years of Recommending Folic Acid**
  - CAPT Jenny Williams, PhD, MSN, MPH, FNP-BC | 3:10 p.m.
- **FAQs About Folic Acid**
  - Shannon Clark, MD, MMS, FACOG | 3:35 p.m.
- **Questions and Answers**
  - Moderated by CAPT Amanda Cohn | 3:50 p.m.




Disclosures

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Folic Acid: The Best Tool to Prevent Neural Tube Defects

MODERATOR

Amanda Cohn, MD (CAPT, USPHS)

OPENING REMARKS

Karen Remley, MD, MBA,MPH, FAAP

PRESENTER

Jennifer Williams, PhD, MSN, MPH, FNP-BC (CAPT, USPHS)

PRESENTER

Shannon Clark, MD, MMS, FACOG

Zoom Poll

Zoom Poll – Knowledge Check

1. Neural tube defects are severe defects of the brain and spine due to failure of the neural tube to close by day ___ of gestation.

a. 14
b. 21
c. 28
d. 35

Zoom Poll – Knowledge Check

2. What is the recommended daily folic acid intake for neural tube defects prevention for persons capable of becoming pregnant, including those with an *MTHFR* variant?

a. 200 µg/day
b. 400 µg/day
c. 1,000 µg/day
d. 2,000 µg/day

Zoom Poll

3. Which form(s) of folate have been scientifically proven to prevent neural tube defects?

a. Folic acid only
b. 5-MTHF only
c. Folic acid and 5-MTHF
d. All forms of folate

What We Have Learned from 30 Years of Recommending Folic Acid

Folic Acid: the Best Tool to Prevent Neural Tube Defects

Jenny Williams, PhD, MSN, MPH, FNP-BC
NTD Surveillance and Prevention Team
Division of Birth Defects and Infant Disorders
Centers for Disease Control and Prevention

Outline

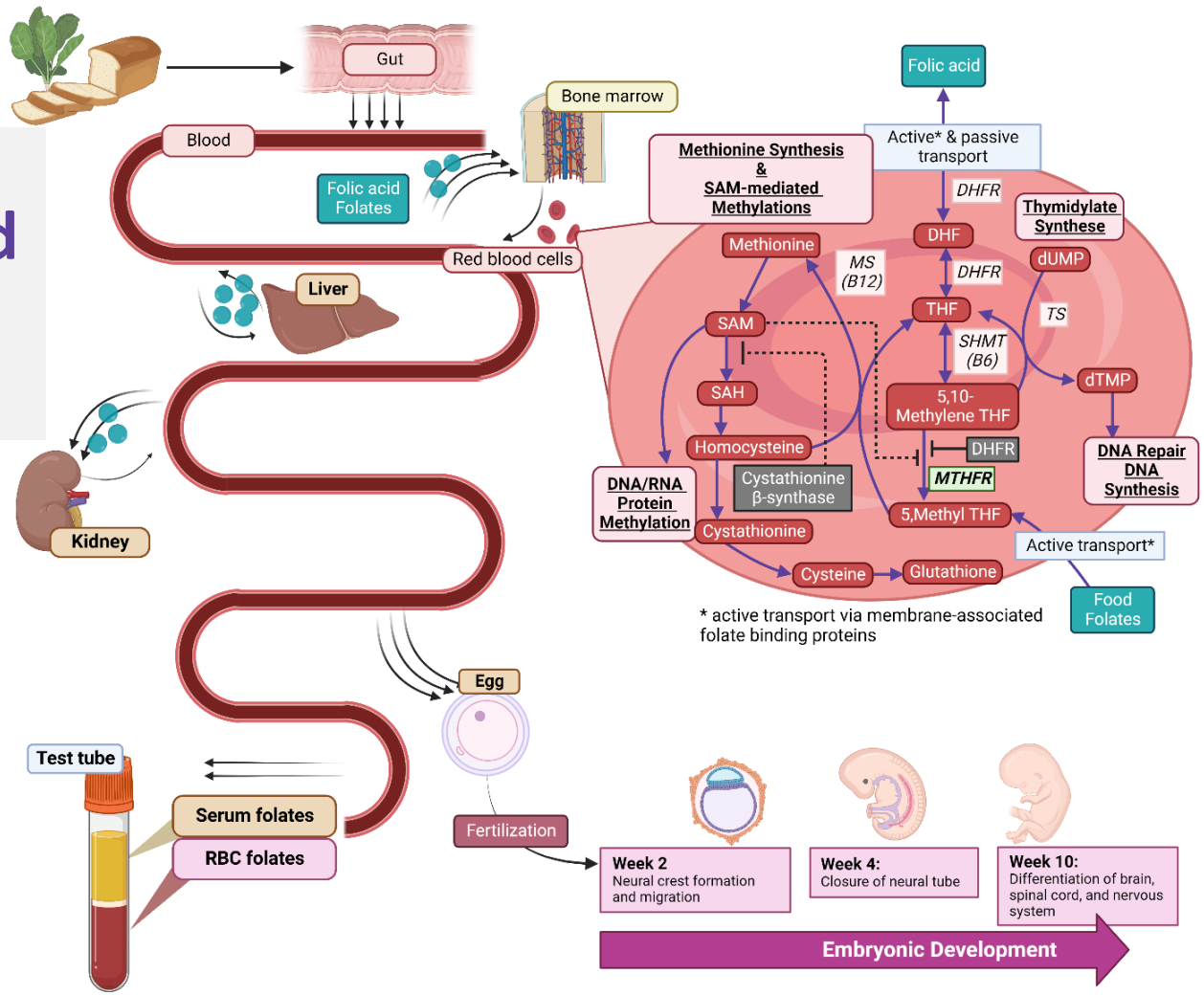
- Background on Folic Acid and Neural Tube Defects (NTD)
- *MTHFR* and Folic Acid
- Sources of Folic Acid and NTD Prevention Strategies
- Addressing Folic Acid Concerns

Background on Folic Acid and Neural Tube Defects

Vitamin B9: Folate and Folic Acid

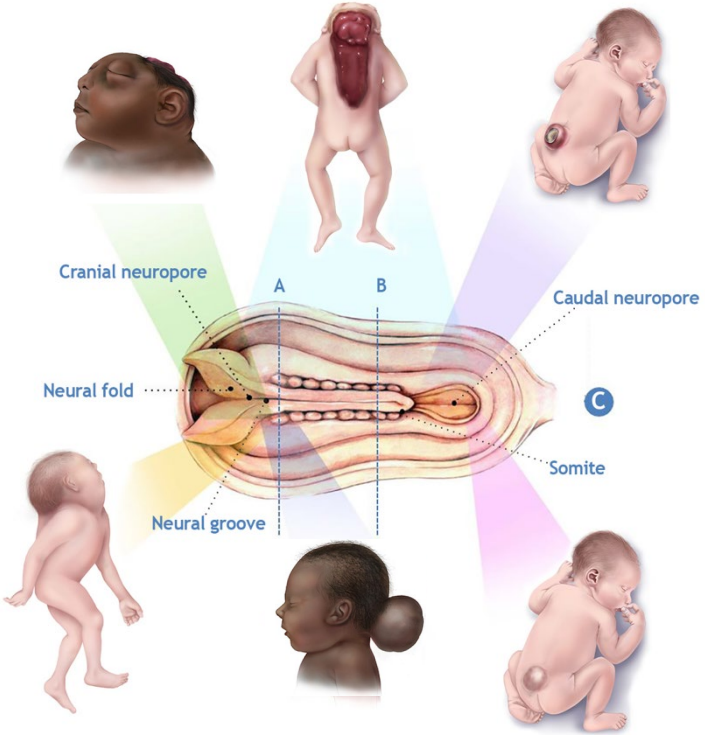
- Folate is a general term for Vitamin B9
- Folate is an umbrella term used to describe its different forms (both natural and synthetic):
  - Food folate
  - Folic acid
  - Dihydrofolate (DHF)
  - Tetrahydrofolate (THF)
  - 5-methyltetrahydrofolate (5-MTHF)
- Folate is critical to basic cellular processes
- Folic acid is a synthetic form of folate that is heat stable
  - Food folate is not as stable to heat or light

Folate Metabolism and One-Carbon Pathway

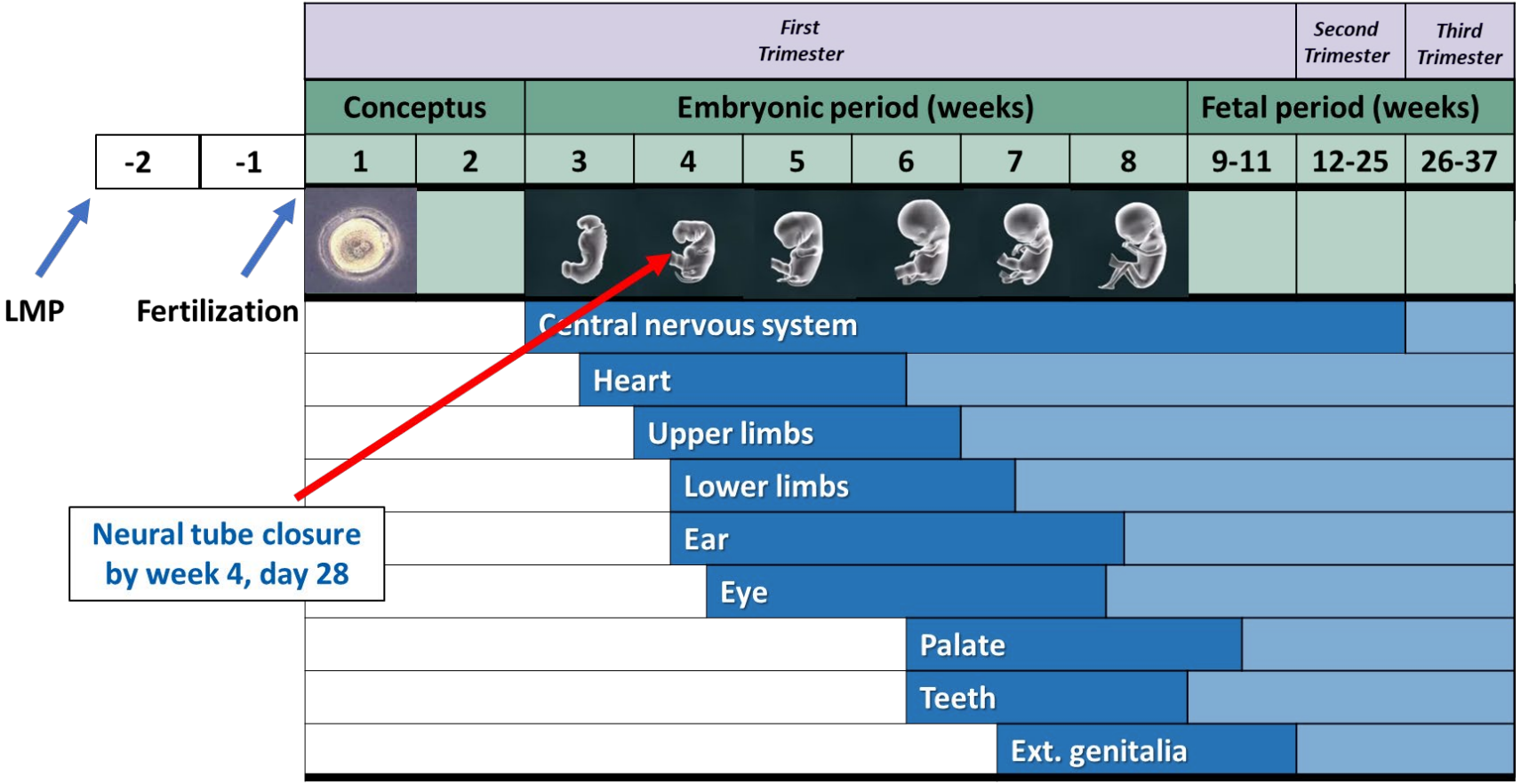


Neural Tube Defects (NTDs)

- Severe defects of brain and spine due to failure of neural tube closure
- Neural tube finishes formation by ***day 28*** of gestation
- 3,000 NTD cases each year in the US
  - Anencephaly and spina bifida comprise 85–90% of NTDs
  - Spina bifida is the most frequently occurring permanently disabling birth defect; lifetime direct cost of care for individual with spina bifida is ~$791,900



Development of Neural Tube During First Trimester

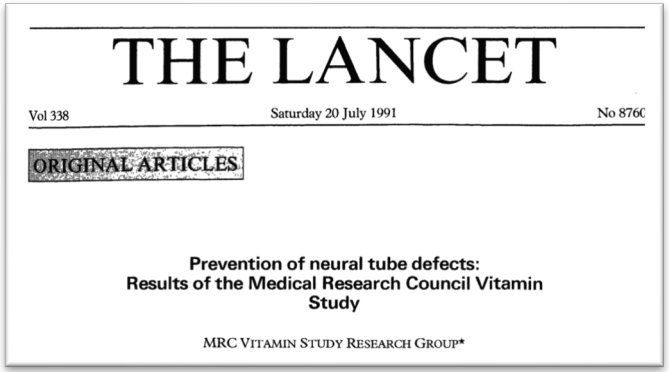


Risk Factors of NTDs

- Genetic causes
  - Single gene disorders
  - Chromosomal disorders
- Non-genetic causes and risk factors
  - Medication use
  - Diabetes
  - Obesity
  - Hyperthermia
  - Race/ethnicity
  - Environmental toxins
  - Vitamin B12 deficiency
  - Folate insufficiency

Many NTD risk factors interact with folate

Randomized Control Trials (RCTs) Demonstrate Folic Acid Prevents NTDs



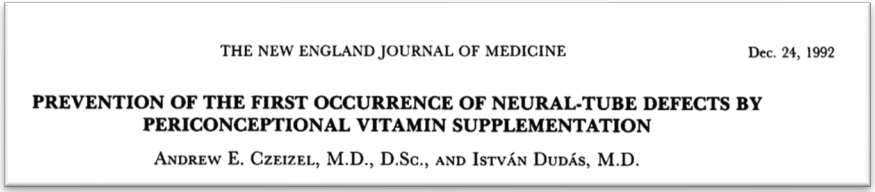
THE LANCET

Vol 338 Saturday 20 July 1991 No 8760

ORIGINAL ARTICLES

Prevention of neural tube defects:
Results of the Medical Research Council Vitamin Study

MRC VITAMIN STUDY RESEARCH GROUP*



THE NEW ENGLAND JOURNAL OF MEDICINE Dec. 24, 1992

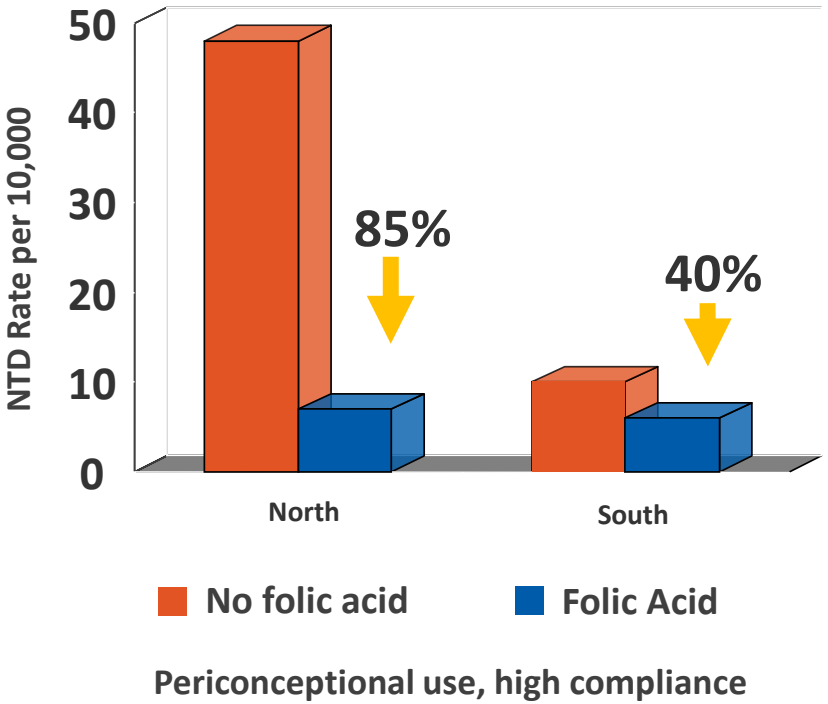
PREVENTION OF THE FIRST OCCURRENCE OF NEURAL-TUBE DEFECTS BY PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

ANDREW E. CZEIZEL, M.D., D.Sc., AND ISTVÁN DUDÁS, M.D.

- 1991: Among women with a **previous NTD-affected pregnancy** (n=1,817)
  - 4,000 mcg (µg)/day supplement containing only folic acid
  - 72% reduction in NTDs
- 1992: Among women **without previous NTD-affected pregnancy** (n=4,753)
  - 800 mcg (µg)/day multivitamin supplement containing folic acid
  - 100% reduction in NTDs

- MRC Vitamin Study Research Group. Lancet. 1991 Jul 20;338(8760):131-7
- Czeizel AE, Dudás I. N Engl J Med. 1992 Dec 24;327(26):1832-5

Evidence from CDC's Community Trial: China (1993–1996)



- Intervention = 400 mcg (µg) folic acid/day
- Women enrolled during premarital examination, included 247,831 pregnancies
- 79% reduction in risk of NTDs
- Percent reduction in NTDs is dependent on baseline rates

Berry RJ, Li Z, Erickson JD, et al. N Engl J Med. 1999 Nov 11;341(20):1485-90. Erratum in: N Engl J Med. 1999 Dec 9;341(24):1864

Folic Acid Recommendations and Fortification Policies

1991

CDC recommended women who have had a previous NTD affected pregnancy consume 4,000 µg one month before through 1st trimester

1992

US Public Health Service recommended that all women who could become pregnant get 400 µg of folic acid each day to prevent NTDs

1998

Institute of Medicine's Food and Nutrition Board recommended that all women who can become pregnant get 400 µg of folic acid each day, in addition to consuming food with folate from a varied diet, to lower the chance of having a baby with an NTD

FDA mandated folic acid fortification of enriched cereal grains

2016

U.S. Preventive Services Task Force 400–800 µg/day of folic acid from supplements

(Grade A: highest level of confidence)

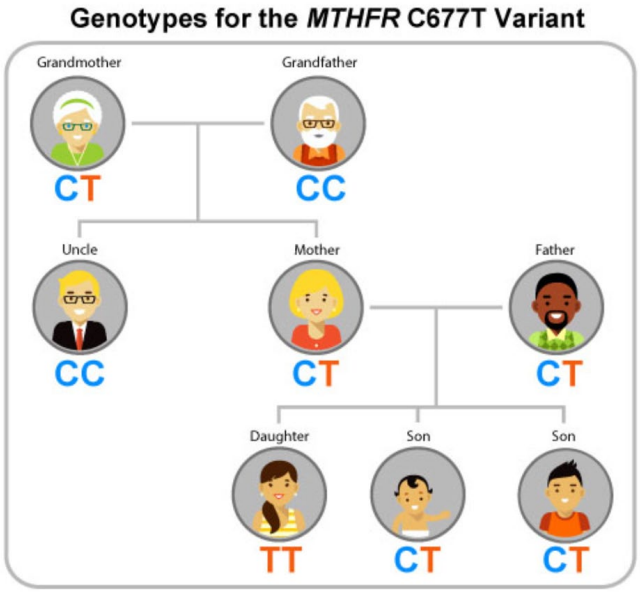
2017

Voluntary folic acid fortification of corn masa flour

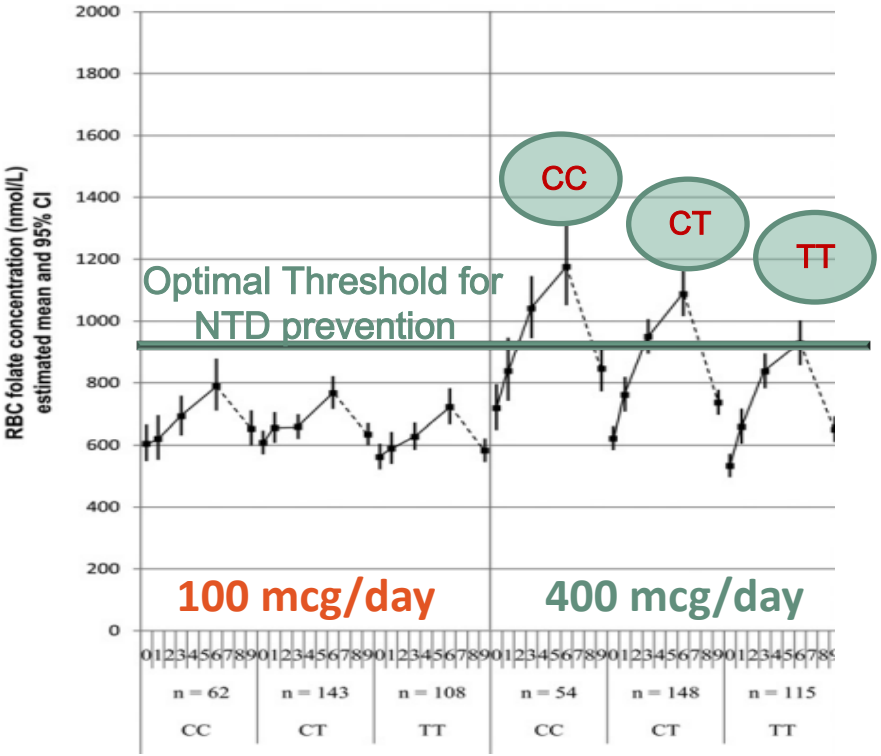
MTHFR and Folic Acid

Methylenetetrahydrofolate Reductase (*MTHFR*)

- The *MTHFR* gene codes for a protein that helps the body process folate
- Common *MTHFR* variants: *MTHFR* 677 CT, *MTHFR* 677 TT, *MTHFR* A1298C
- When consuming the same amount of folic acid, people with the *MTHFR* 677 TT genotype have an average blood folate concentration that is only slightly lower (about 16% lower) than people with the *MTHFR* 677 CC genotype
- Individuals with one of these *MTHFR* variants can safely and effectively process all types of folate, including folic acid



Clinical Significance of *MTHFR* Variant



- Intervention:
  - Women consumed different dosages of folic acid for 6 months
- Measurements:
  - Women genotyped for *MTHFR* C667T
  - Blood samples at 0, 1, 3, 6 months of folic acid supplement and then 3 months after stopping
- Findings:
  - 100 mcg/day: NONE of the genotypes made the optimal threshold of blood folate for NTD prevention
  - 400 mcg/day: ALL of the genotypes made the optimal threshold by 6 months
  - After stopping folic acid supplementation, blood folate dropped under optimal threshold
    - Need constant intake

Clinical Significance of *MTHFR* Variant

- Routine screening for the *MTHFR* C677T variant is not recommended by the American College of Obstetricians and Gynecologists (ACOG)
  - *MTHFR* C677T variant is associated with some disease outcomes, e.g., cancer and NTDs, highlighting the importance of adequate folate status
- All persons capable of pregnancy, regardless of *MTHFR* genotype status, are encouraged to consume 400 µg of folic acid per day
  - Consuming this amount of folic acid increases blood folate concentration to optimal threshold for NTD prevention for all genotypes

Sources of Folic Acid and NTD Prevention Strategies

Sources of Folate/Folic Acid

Diet…natural foods such as vegetables, fruits, beans, yeast, liver

Pills…folic acid-containing dietary supplements

Fortification…folic acid added to foods

- **Mandatory** - enriched cereal grains, e.g., flour, rice, pasta
- **Voluntary** – breakfast cereals, corn masa flour

Dietary Approach: Deliver Folate to Populations

- Possible but difficult
- US women consume ~200 µg folate/day

- Advantages
  - Other benefits of healthy diet
- Disadvantages
  - Availability limited
  - Higher cost of folate-rich foods
  - Absorption and bioavailability
  - Requires sustained public education
  - Requires behavior change

Supplementation Approach: Deliver Folic Acid to Populations

- Most multivitamin supplements contain 400 µg folic acid
- 20–25% U.S. women consume 400 µg folic acid

- Advantages
  - Excellent bioavailability
- Disadvantages
  - Relative cost of tablets
  - Requires sustained public education
  - Requires behavior change
  - 50% unplanned pregnancies

Supplement and Multivitamin Labels

- If a multivitamin states it contains folate, it does not mean the form of folate is folic acid
- Rise in multivitamins using other forms of folate, e.g., 6S-5-methyltetrahydrofolate
  - Folic acid is the only form of folate shown in randomized control trials to prevent NTDs
  - Unknown if other folate forms are effective for NTD prevention and at what dose and if co-factors are needed
- Check supplement labels for which form of folate is being used
- Taking more than the recommended dose of folic acid is not necessarily better for occurrent NTD prevention. Higher doses are only recommended for specific medical conditions, e.g., previous affected pregnancies, interactions with certain medications

Supplement and Multivitamin Labels

Supplement Facts

Serving Size 1 Softgel

Amount Per Softgel	% Daily Value for Pregnant Women and Lactating Women
Calories 5	
Vitamin A (as Beta Carotene) 770 mcg	59%
Vitamin C (as Ascorbic Acid) 85 mg	71%
Vitamin D_3 (as Cholecalciferol) 25 mcg (1000 IU)	167%
Vitamin E (as d-Alpha Tocopherol) 15 mg	79%
Vitamin K (as Phytonadione) 90 mcg	100%
Thiamin (as Thiamine Mononitrate) 1.4 mg	100%
Riboflavin 1.4 mg	88%
Niacin (as Niacinamide) 18 mg	100%
Vitamin B_6 (as Pyridoxine Hydrochloride) 1.9 mg	95%
Folate 1330 mcg DFE (800 mcg Folic Acid)	222%
Vitamin B_{12} (as Cyanocobalamin) 5.2 mcg	186%
Biotin 30 mcg	86%
Pantothenic Acid (as d-Calcium Pantothenate) 6 mg	86%
Calcium (as Calcium Carbonate) 150 mg	12%
Iron (as Ferrous Fumarate) 27 mg	100%
Iodine (as Potassium Iodide) 150 mcg	52%
Magnesium (as Magnesium Oxide) 45 mg	11%
Zinc (as Zinc Oxide) 11 mg	85%
Omega-3 Fatty Acids (from Fish Oil Concentrate)†† 260 mg	*
Omega-3 Docosahexaenoic Acid (DHA)†† 200 mg	*
Omega-3 Eicosapentaenoic Acid (EPA)†† 60 mg	*

*Daily Value not established.

SUGGESTED USE:
Adults, take 1 softgel daily with water and a meal for optimal absorption.

Store tightly closed, in a cool, dry place, out of reach of children.
Do not use if imprinted seal under cap is broken or missing.

CAUTION:
If you are taking medication or have blood clotting issues, consult your physician before use.

✓ **No Artificial Flavors**
✓ **Gluten Free**

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

OTHER INGREDIENTS:
Gelatin, Glycerin, Rapeseed Lecithin, Soybean Oil, Water, Dibasic Calcium Phosphate, Yellow Beeswax, Tocopherols, Resin, Ascorbyl Palmitate.

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West Hills, CA 91309-9903, USA
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USP has tested and verified ingredients, potency and manufacturing process.
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†† As ethyl esters

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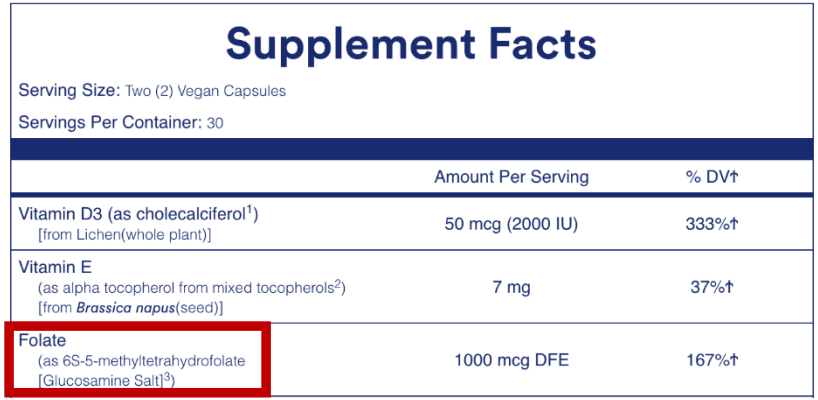


Supplement Facts

Serving Size: Two (2) Vegan Capsules

Servings Per Container: 30

	Amount Per Serving	% DV†
Vitamin D3 (as cholecalciferol[1]) [from Lichen(whole plant)]	50 mcg (2000 IU)	333%†
Vitamin E (as alpha tocopherol from mixed tocopherols[2]) [from *Brassica napus*(seed)]	7 mg	37%†
Folate (as 6S-5-methyltetrahydrofolate [Glucosamine Salt][3])	1000 mcg DFE	167%†

Nutrition Label Update

1 mcg (µg) of folic acid = 1.67 mcg (µg) dietary folate equivalents (DFE)

	Recommended mcg DFE	Recommended mcg Folic Acid	% Daily Value (DV)
To Prevent Anemia	400 mcg DFE	240 mcg folic acid	100%
To Prevent NTDs	667 mcg DFE	400 mcg folic acid	167%

% daily value (DV) based on new Nutrition Facts and Supplement Facts labels starting January 1, 2021.

Nutrition Label Update

Old Label

Supplement Facts

	Amount Per Serving	% Daily Value
Folic Acid	400 mcg	100%
Vitamin B12	6 mcg	100%
Pantothenic	5 mg	50%
Calcium	450 mg	45%
Iron	18 mg	100%
Magnesium	50 mg	12%
Zinc	15 mg	100%

New Label

Supplement Facts

Serving Size 1 Tablet

	Amount Per Serving	% Daily Value
Folate	667 mcg DFE (400 mcg folic acid)	167%
Vitamin B12	6 mcg	250%
Pantothenic Acid	10 mg	200%
Calcium	200 mg	15%
Iron	18 mg	100%
Magnesium	100 mg	24%
Zinc	11 mg	100%

Fortification Approach: Deliver Folic Acid to Populations

- "Enriched" foods in the U.S. now contain 140 micrograms folic acid per 100 grams of grain product

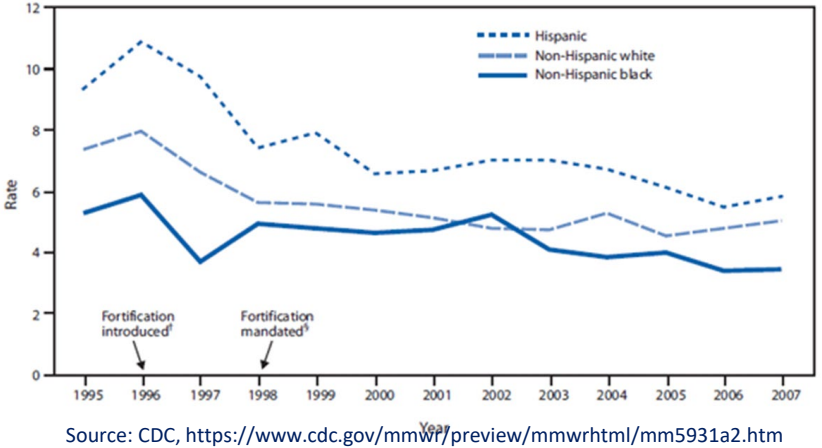
- Advantages
  - Good bioavailability
  - Inexpensive
  - Wide coverage
  - Minimal behavior change required
  - No pregnancy planning

- Disadvantages
  - Wide variation of staple foods
  - Limited effectiveness with smaller amounts added to foods

Impact of Mandatory Folic Acid Fortification and NTDs

- Overall, 35% reduction in occurrence of NTDs after mandatory folic acid fortification in the United States
- Decline in prevalence of severe upper-level lesion cases of spina bifida by 72% after mandatory folic acid fortification while prevalence of less severe, lower-level lesions remained relatively stable

Neural tube defect prevalence by race/ethnicity and fortification period status

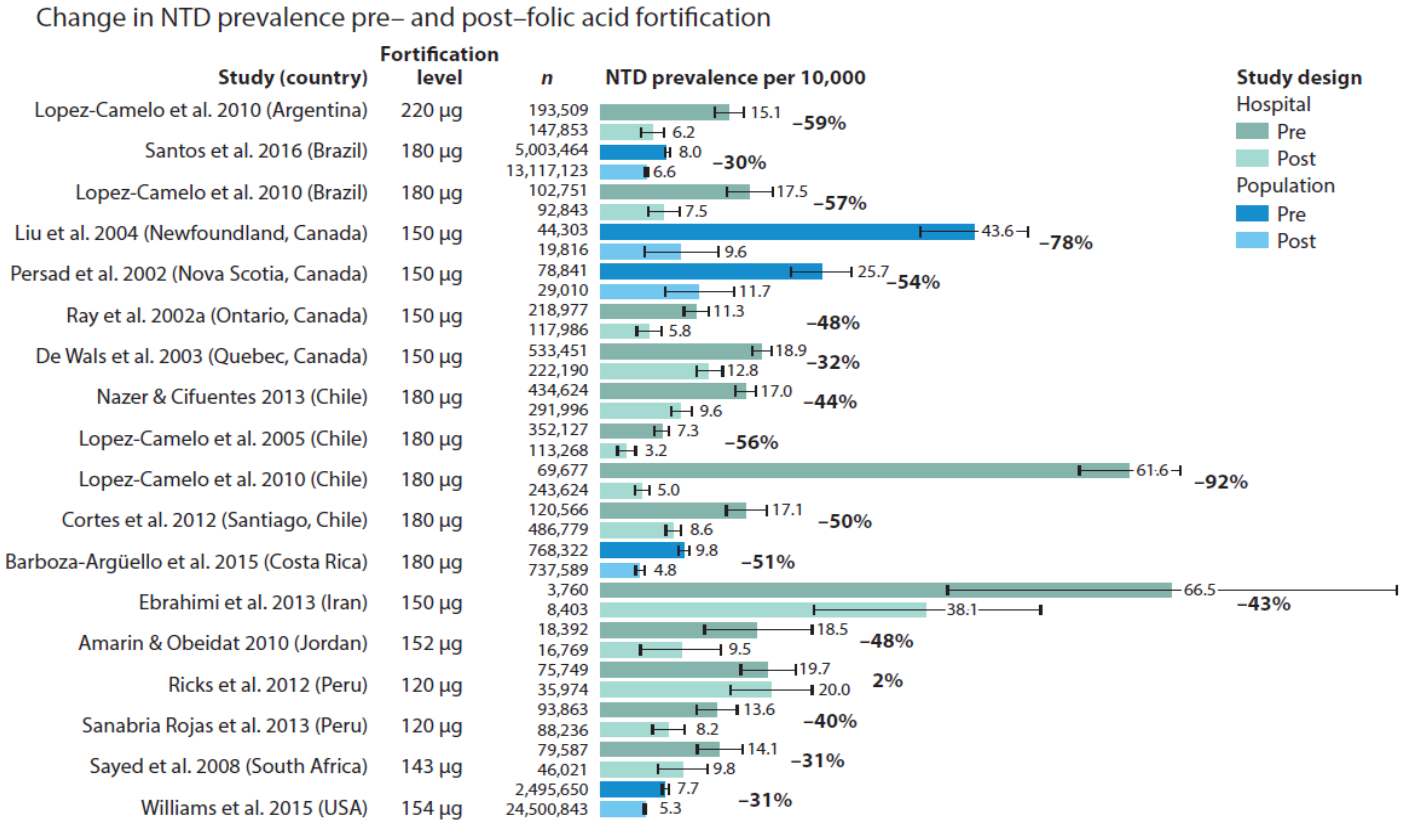


Source: CDC, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a2.htm

* Anencephaly and spina bifida only, some programs without prenatal ascertainment

- Williams J, et al. MMWR. 2015 Jan 16;64(1):1-5.
- Mai CT, et al. J Pediatr. 2022 Jun 27;S0022-3476(22)00597-2.

Changes in NTD Prevalence Before and After Mandatory Folic Acid Fortification



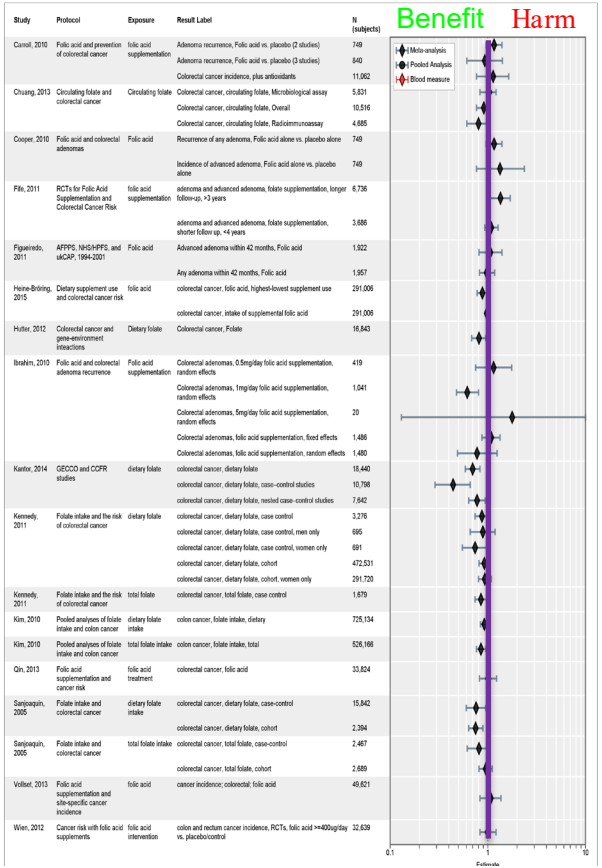
Addressing Folic Acid Concerns

Summary of Folic Acid Safety Issues Discussed in Comprehensive, Evidence-Based Folic Acid Safety Reviews of Six Major International Bodies

	Food and Drug Administration, Federal Register	Institute of Medicine	Scientific Advisory Committee on Nutrition, UK	Food Standards Australia New Zealand	Food Safety Authority Ireland	Health Council of the Netherlands
Indirect Effects of Folic Acid on **Masking of Vitamin B12 Deficiency**	X	X	X	X	X	X
Circulating **Unmetabolized Folic Acid**	X		X	X	X	X
DNA Methylation and Synthesis		X	X	X	X	
Direct Effects of Folic Acid on **Anemia, Cognition, and Interaction with Vitamin B12**	X	X	X	X	X	X
Antenatal Folic Acid in Populations with **Low Vitamin B12 Status**	X	X	X	X		X
Total Cancer or Multiple Cancer		X	X	X	X	X
Colorectal Cancer		X	X	X	X	X
Multiple Births or Twinning			X	X	X	X
Spontaneous Abortions (**Miscarriage**)		X		X		
Folate-Drug Interactions	X	X	X	X	X	

Pooled Studies on cancer, colorectal cancer, and diabetes-related outcomes

- All cancer, pooled: Folic Acid - All Cancer Pooled and Meta-analyses (2015) | HAWC (hawcproject.org)
- Colorectal cancer: https://hawcproject.org/summary/data-pivot/assessment/94/draft-colorectal-cancer/
- Diabetes-related outcomes: https://hawcproject.org/summary/data-pivot/assessment/68/draft-all-non-ratio-based-results-correlation-regr/



Study	Protocol	Exposure	Result Label	N (subjects)
Cantoll, 2010	Folic acid and prevention of colorectal cancer	folic acid supplementation	Adenoma recurrence, Folic acid vs. placebo (2 studies)	749
			Adenoma recurrence, Folic acid vs. placebo (3 studies)	840
			Colorectal cancer incidence, plus antioxidants	11,062
Chuang, 2013	Circulating folate and colorectal cancer	Circulating folate	Colorectal cancer, circulating folate, Microbiological assay	5,831
			Colorectal cancer, circulating folate, Overall	10,516
			Colorectal cancer, circulating folate, Radioimmunoassay	4,685
Cooper, 2010	Folic acid and colorectal adenomas	Folic acid	Recurrence of any adenoma, Folic acid alone vs. placebo alone	749
			Incidence of advanced adenoma, Folic acid alone vs. placebo alone	749
Fife, 2011	RCTs for Folic Acid Supplementation and Colorectal Cancer Risk	folic acid supplementation	adenoma and advanced adenoma, folate supplementation, longer follow-up, >3 years	6,736
			adenoma and advanced adenoma, folate supplementation, shorter follow up, <4 years	3,686
Figueiredo, 2011	AFPPS, NHS/HPFS, and uACAP, 1994-2001	Folic acid	Advanced adenoma within 42 months, Folic acid	1,922
			Any adenoma within 42 months, Folic acid	1,957
Heine-Bröring, 2015	Dietary supplement use and colorectal cancer risk	folic acid	colorectal cancer, folic acid, highest-lowest supplement use	291,006
			colorectal cancer, intake of supplemental folic acid	291,006
Hutter, 2012	Colorectal cancer and gene-environment interactions	Dietary folate	Colorectal cancer, Folate	16,843
Ibrahim, 2010	Folic acid and colorectal adenoma recurrence	Folic acid supplementation	Colorectal adenomas, 0.5mg/day folic acid supplementation, random effects	419
			Colorectal adenomas, 1mg/day folic acid supplementation, random effects	1,041
			Colorectal adenomas, 5mg/day folic acid supplementation, random effects	20
			Colorectal adenomas, folic acid supplementation, fixed effects	1,480
			Colorectal adenomas, folic acid supplementation, random effects	1,480
Kantor, 2014	GECCO and CCFR studies	dietary folate	colorectal cancer, dietary folate	18,440
			colorectal cancer, dietary folate, case-control studies	10,798
			colorectal cancer, dietary folate, nested case-control studies	7,642
Kennedy, 2011	Folate intake and the risk of colorectal cancer	dietary folate	colorectal cancer, dietary folate, case control	3,276
			colorectal cancer, dietary folate, case control, men only	695
			colorectal cancer, dietary folate, case control, women only	691
			colorectal cancer, dietary folate, cohort	472,531
			colorectal cancer, dietary folate, cohort, women only	291,720
Kennedy, 2011	Folate intake and the risk of colorectal cancer	total folate	colorectal cancer, total folate, case control	1,679
Kim, 2010	Pooled analyses of folate intake and colon cancer	dietary folate intake	colon cancer, folate intake, dietary	725,134
Kim, 2010	Pooled analyses of folate intake and colon cancer	total folate intake	colon cancer, folate intake, total	526,166
Qin, 2013	Folic acid supplementation and cancer risk	folic acid treatment	colorectal cancer, folic acid	33,824
Sanjoaquin, 2005	Folate intake and colorectal cancer	dietary folate intake	colorectal cancer, dietary folate, case-control	15,842
			colorectal cancer, dietary folate, cohort	2,394
Sanjoaquin, 2005	Folate intake and colorectal cancer	total folate intake	colorectal cancer, total folate, case-control	2,467
			colorectal cancer, total folate, cohort	2,689
Voltset, 2013	Folic acid supplementation and site-specific cancer incidence	folic acid	cancer incidence; colorectal; folic acid	49,621
Wien, 2012	Cancer risk with folic acid supplements	folic acid intervention	colon and rectum cancer incidence, RCTs, folic acid >=400ug/day vs. placebo/control	32,639

Addressing Folic Acid Concerns

- Folic acid taken at or up to the recommended amount of 400 micrograms per day (mcg/day) has not been shown to be harmful. As new studies become available, they are assessed and weighted against the totality of the evidence.
- Specific answers to additional questions are available at www.cdc.gov/ncbddd/folicacid/faqs.

Summary

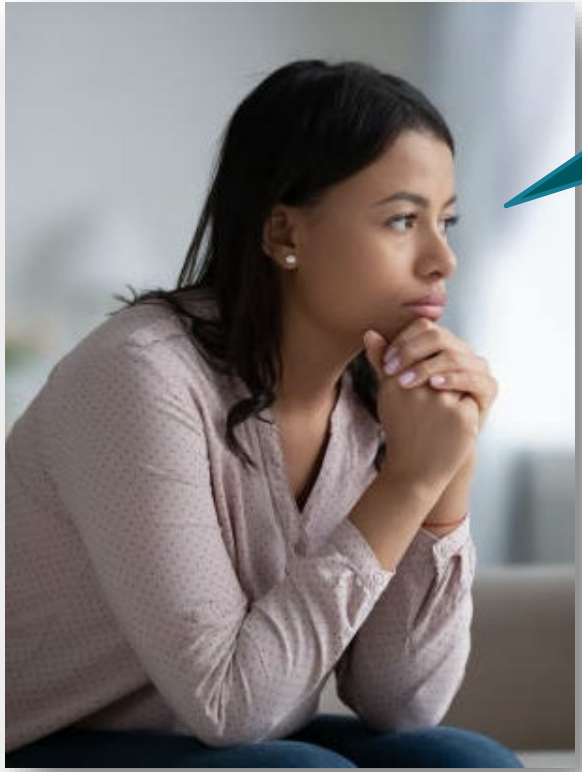
- Folic acid is effective in preventing NTDs across populations
  - 1,300 babies in the US born each year without NTDs
  - Annual cost savings of $603M
- Folic acid is the only form of folate shown to prevent NTDs
- All persons capable of becoming pregnant should consume 400 µg/day, including those with an *MTHFR* variant

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

FAQS ABOUT
FOLIC ACID

SHANNON M. CLARK, MD
PROFESSOR MATERNAL-FETAL MEDICINE
CDC Webinar September 14, 2022

utmb Health



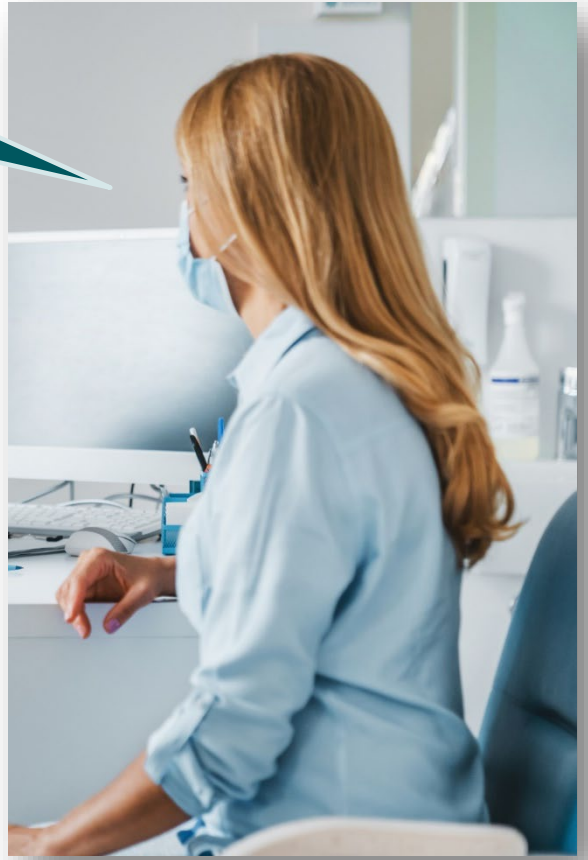
Are folate & folic acid the same thing?

- The terms “folate” and “folic acid” are often used interchangeably, even though they are different.
  - Folate is vitamin B9 naturally present in many foods, including vegetables, fruits and fruit juices, beef liver, nuts and beans and peas.
  - Folic acid (FA) is the synthetic form of vitamin B9 used in a multivitamin, prenatal vitamin, or single supplement and fortified foods.
- Types of folate other than folic acid found in supplements (such as 5-MTHF or methylfolate) are different from the folate found in fruits and vegetables, even if the nutrition label claims it is "natural”.

SOURCE: CDC &FDA

How do I know if my prenatal vitamin has folic acid?

- The microgram (mcg) dietary folate equivalents (DFE) is the unit of measure for folate on the new Nutrition Facts or Supplement Facts label.
  - The measure of mcg DFE is used because the body has an easier time absorbing folic acid than folate.

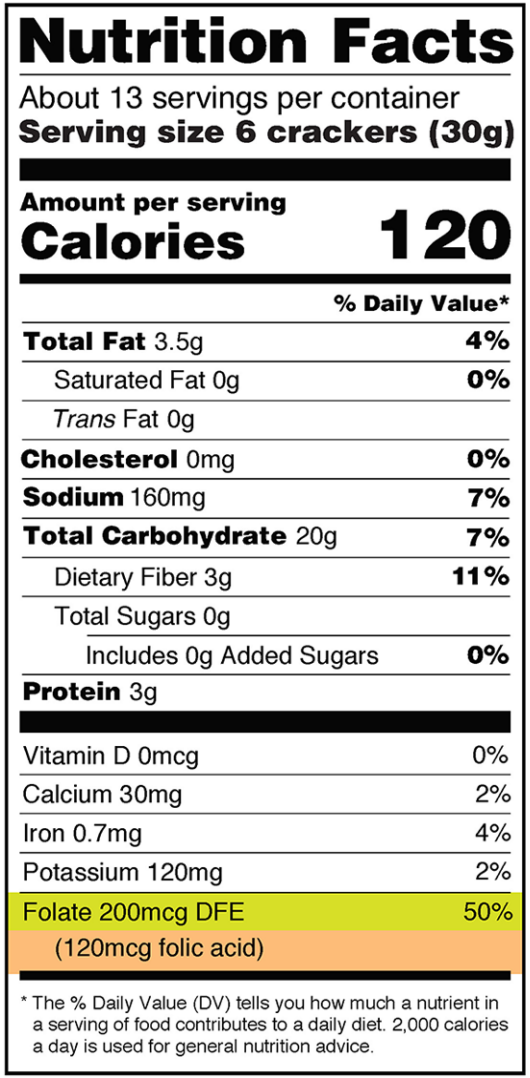


REFRESH: **Nutrition Facts or Supplement Facts label**

- A % daily value (DV) is shown for the total amount of folate in a product, and if any of the total folate comes from folic acid, that amount of folic acid is listed in mcg in parentheses.

1. Folate is shown as mcg DFE and as a %DV.
2. Folic acid is shown in parenthesis and is important for individuals who could become pregnant.

- For individuals who could become pregnant, look for the amount of **folic acid in mcg** listed in the parentheses on the label.



Nutrition Facts

About 13 servings per container
Serving size 6 crackers (30g)

Amount per serving
Calories **120**

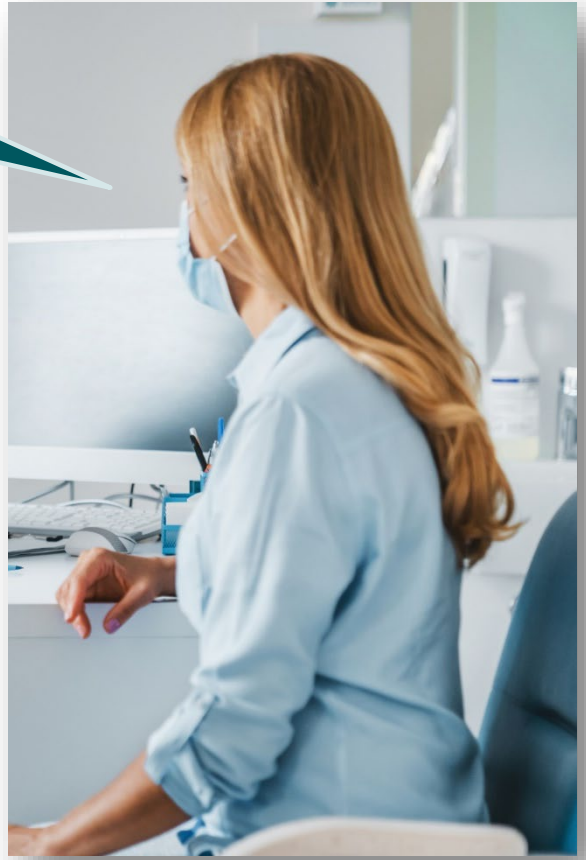
	% Daily Value*
Total Fat 3.5g	**4%**
Saturated Fat 0g	**0%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Total Carbohydrate 20g	**7%**
Dietary Fiber 3g	**11%**
Total Sugars 0g	
Includes 0g Added Sugars	**0%**
Protein 3g	
Vitamin D 0mcg	0%
Calcium 30mg	2%
Iron 0.7mg	4%
Potassium 120mg	2%
Folate 200mcg DFE	50%
(120mcg folic acid)	

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

How do I know if my prenatal vitamin has folic acid?

- The mcg dietary folate equivalents (DFE) is the unit of measure for folate on the new Nutrition Facts or Supplement Facts label.
  - The measure of mcg DFE is used because the body has an easier time absorbing folic acid than folate.

If a product's label lists %DV for folate but does not show mcg of folic acid in parentheses that means that folic acid **has not** been added to the product.



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Selected risk factors for a neural tube defect:

- A previous pregnancy affected by an NTD or with an NTD in either parent
- Immediate family history of NTDs
- Use of certain antiseizure medications (e.g., valproic acid or carbamazepine)

Do I need high dose folic acid supplementation?

- If you have risk factors for NTD, consume 400 mcg/0.4 mg of FA supplementation each day, even when not planning to become pregnant.
  - If you are planning to become pregnant and depending on the risk factor, take 1000 or 4000 mcg /1 mg or 4 mg of FA supplementation each day, starting 1-3 months before becoming pregnant and continuing through the first 3 months of pregnancy, depending on the risk factor.
- The dose can be reduced to 400 mcg/0.4 mg after the first trimester since the reason for therapy (prevention of NTDs) is no longer relevant.

SOURCE: FOLIC ACID SUPPLEMENTATION TO PREVENT RECURRENT NEURAL TUBE DEFECTS: 4 MILLIGRAMS IS TOO MUCH, FETAL DIAGNOSIS AND THERAPY, OCTOBER 2018 & USPSTF. FOLIC ACID SUPPLEMENTATION FOR THE PREVENTION OF NEURAL TUBE DEFECTS: US PREVENTIVE SERVICES TASK FORCE RECOMMENDATION STATEMENT. JAMA. 2017

Folic acid supplementation recommendations by indication

Indication for supplementation	Dose (daily)	Start (minimum)	Duration*	Recommended by
High risk				
Prior open NTD in offspring of either parent or personal history of open NTD in either parent[1,2]	4 mg	Three months PTC	12 weeks	SOGC, ACOG
Moderate risk				
Personal or family history of folate-sensitive congenital anomaly other than NTD[2]	1 mg	Three months PTC	12 weeks	SOGC
Family history of NTD (first- or second-degree relative)[2]	1 mg	Three months PTC	12 weeks	SOGC
Type I or II diabetes[2,4,5]	1 mg	Three months PTC	12 weeks	SOGC
	0.4 mg	One month PTC	12 weeks	ADA, ACOG
Maternal gastrointestinal malabsorption[2]	1 mg	Three months PTC	12 weeks	SOGC
Medical conditions associated with risk (advanced liver disease, dialysis, alcohol overuse)[2]	1 mg	Three months PTC	12 weeks	SOGC
Low risk				
Pregnancy or potential for pregnancy[1,3,6]	0.4 mg	At least one month PTC	12 weeks	ACOG, CDC
	0.4 to 0.8 mg	One month PTC	First two to three months of pregnancy	USPSTF

ACOG: American College of Obstetricians and Gynecologists
SOGC: Society of Obstetricians and Gynaecologists of Canada
ADA: American Diabetes Association
USPSTF: United States Preventive Services Task Force

SOURCE: FOLIC ACID SUPPLEMENTATION IN PREGNANCY, UP TO DATE

Does folic acid help with other things in pregnancy?

- Some **congenital malformations** (e.g., cleft lip/palate, congenital heart defects, limb reduction defects, urinary tract defects, and congenital hydrocephalus) may be **folate-sensitive**.
  - Animal studies also provide some experimental support for folic acid supplementation to reduce the risk of cleft lip/palate from concurrent exposure to procarbazine, a folic acid inhibitor.

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Does folic acid help with other things in pregnancy?

A higher dose (1000 mcg/1 mg per day) of periconceptional/first-trimester folic acid supplementation can be considered for those with a history of the following malformations in themselves or their partner, a prior offspring, or a first- or second-degree relative:

- Cleft lip/palate
- Congenital heart defects
- Limb reduction defects
- Urinary tract defect

What happens if I take too much folic acid? Is it harmful?

- Folic acid is considered nontoxic, even at very high doses because it does not collect in fat, but is water soluble.
  - Any amount of folic acid that is not used by the body goes through the kidneys, into the urine, and out of the body.
- When folic acid supplementation is excessive, unmetabolized folic acid can accumulate in the serum.
  - Studies in both nonpregnant and pregnant persons show that folic acid doses greater than ~800–1,000 mcg/day result in detectable levels of unmetabolized folic acid in both maternal and fetal blood samples.
  - **The risks of higher levels of folic acid supplementation are believed to be minimal** because unused folic acid in the blood goes to the kidneys and leaves the body in urine.

SOURCE: PUBLIC HEALTH FAILURE IN THE PREVENTION OF NEURAL TUBE DEFECTS: TIME TO ABANDON THE TOLERABLE UPPER INTAKE LEVEL OF FOLATE. PUBLIC HEALTH REV, 2018

Can I still take folic acid if I have an MTHFR gene variant?

- You may have heard that if you have an *MTHFR* gene variant, you should take other types of folate, but **this is not true**!
- Prescribing higher doses of folic acid supplementation because of an *MTHFR* gene variant is not necessary.
  - The routine universal prophylaxis dosing (at least 400mcg/0.4 mg/day) is recommended.
- **Testing for *MTHFR* gene variants is not recommended** as routine folic acid supplementation at 400mcg/0.4 mg per day will adequately increase red cell and serum folate concentrations, whether or not the person has an *MTHFR* gene variant.

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BOTTOM LINE: *MTHFR* GENE VARIANT & FOLIC ACID

- There are no obstetrical indications for testing anyone who is trying to conceive or pregnant for *MTHFR* gene mutations.
- Studies have shown that a person who consumes 400 mcg/0.4 mg of FA each day generally has enough folate in their blood to help prevent NTDs, regardless of *MTHFR* C677T genotype (CC, CT, or TT)

- Despite the scientific consensus, some healthcare professionals are causing many people to question whether they should be consuming any folic acid at all.
- Medical experts worry that these individuals are urging people who could become pregnant to avoid vital folic acid supplementation, putting unborn babies at unnecessary risk for NTDs.
- **Folic acid is the only form of folate proven to prevent NTDs.**

SOURCE: CDC &FDA

THANK YOU

SHANNON M. CLARK, MD

- https://www.babiesafter35.com

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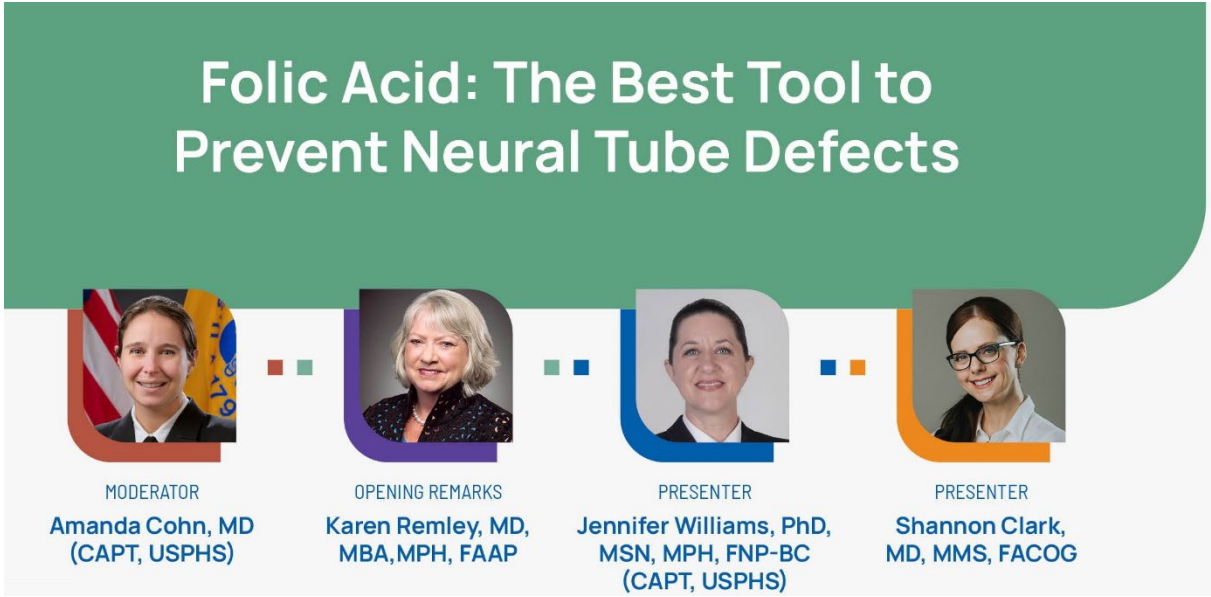
Questions and Answers



Continuing Education (CE)

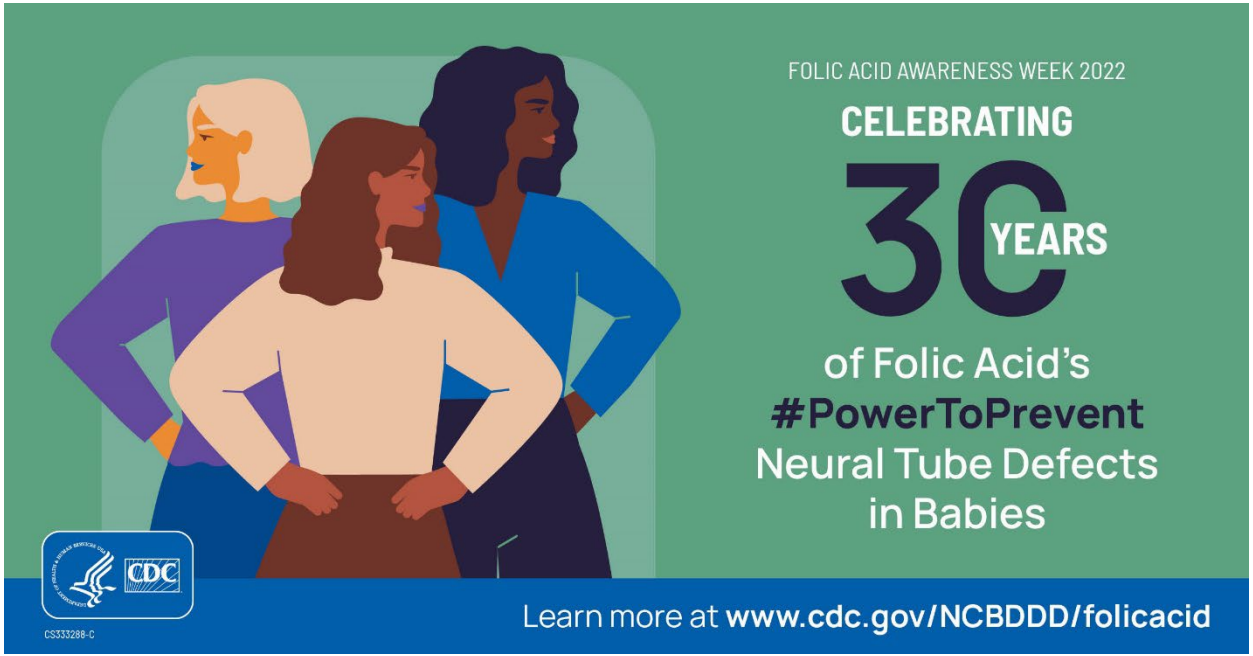
To receive free CME, CNE, CEU, CECH, CPH credit/hour for WC4615 - Folic Acid: the Best Tool to Prevent NTDs:

1. Go to www.cdc.gov/getCE
2. Follow the outlined “9 Simple Steps to Earn CE” by October 17, 2022
3. The course access code is: **folicacid2022**

To receive CPE (Dietitians and Dietetic Technicians, Registered):

1. Complete the evaluation at bit.ly/FolicAcidCPE
2. Contact Benjamin.Hartley@azdhs.gov for questions about earning CPE credit approved by CDR.

Thank you



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.