





Can we prevent Cleft Lip and Palate?



To parents of those special children who were born with cleft lip and palate

and

To those special adults who have overcome all hardship related to their cleft and are ready to start a family of their own



Jes, Ne Can!



There is enough scientific evidence strongly suggesting that a significant proportion of cleft lip and palate

is preventable





You, the parent of a child with cleft lip and palate, know better than anybody else how special your son or daughter is.

And, as all of us, you want the best for your child. Your child is unique, different from others because of the cleft. We would like to share our present knowledge about clefts, how they develop, the possible causes, and how we can prevent them.

Before you begin reading this pamphlet, please remember, you are not to blame for your child's cleft.

As you will see, finding what caused the cleft to develop is not a simple task, nor is there a simple solution.

There are some general principles, either known for some time or discovered recently, which could substantially reduce the risk of developing cleft lip and palate.

These principles may be of interest to you if you plan to have another child, if you would like to know about risk for your child's children, or if you have a cleft yourself and are thinking about starting a family.

It is just like taking your driving test for the first time. First, you had to understand the general rules of driving, then apply them when you were behind the steering wheel.

You did all this because you wanted to transport yourself somewhere while preventing accidents and injury.

The prevention of clefts is similar. You have to know what can happen "if..." in order to prevent it from happening.

The following paragraphs will walk you through several principles necessary for understanding the prevention of orofacial clefts.

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About Clefts

How Clefts Develop

- Orofacial clefts (OFC) cleft lip (CL), cleft lip and palate (CLP), and cleft palate (CP) - are caused by interactions between genetic and environmental factors.
- It is understood that genetic factors create a "susceptibility" for clefts. When environmental factors (triggers) interact with a genetically susceptible genotype, a cleft develops in an early stage of development.
- Mechanistically, a cleft develops when embryonic parts called "*processes*" (which are programmed to join with each other and form an individual part of the embryo) do not reach each other in time, and an "open space" (cleft) between them persists.
- *Processes* "grow into an open space" through of cellular multiplication, touch each other, and fuse together.
- In general, any influence that could prevent the *processes* from reaching each other, by slowing down the multiplication of cells, stopping this development for a while, or killing the cells already there, would cause persistence of "open space" = cleft.

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Birth Prevalence

- One in about every 600 babies is born with cleft lip with or without cleft palate (CL±P) or with cleft palate only (CP). The birth prevalence varies in different ethnicities, being highest in American Indians. In studies around the world the highest prevalence is observed in locations with hard living conditions and poor nutrition.
- Every 4 minutes, somewhere in the world a baby with a cleft is born.
- In our study of 2.5 million birth (years 1983-1993) in California we observed 1 baby born with a cleft in 566 newborns.

Prevalence of nonsyndromic orofacial clefts and Pierre Robin sequence in 2,509,881 California births (years 1983-1993)

Type of cleft	Prevalence per 1,000 births		
Type of cleft	Number	Rate	95% CI
Cleft lip (CL)	718	0.29	0.27, 0.31
Cleft lip and palate (CLP)	1217	0.48	0.46, 0.51
Cleft palate only (CP)	784	0.31	0.29, 0.34
CI = Confidence Interval		Tolarova and	d Cervenka, 1998



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Every day in the USA, 11 babies are born with CL±P and 6 are born with CP. In the recent study of national prevalence of birth defects

Prevalence of cleft lip and palate adapted from *National population-based estimates for major birth defects, 2010-2014* (Mai et al 2019).

Prevalence per 1,000 births			
Number	Rate	95% CI	
180	0.35	0.34, 0.37	
346	0.67	0.65,0.69	
307	0.59	0.57, 0.61	
	Preval <i>Number</i> 180 346 307	Prevalence per 1,0 Number Rate 180 0.35 346 0.67 307 0.59	

CI = Confidence Interval

Mai et al.2019

Cost

- The lifetime cost of medical treatment for each child born with an orofacial cleft is about \$100,000 in the USA
- Thus, when 17 babies are born with orofacial clefts each day (6,222 each year), the lifetime medical cost for children born every year represents over \$622 million





Risk of Recurrence

When an individual with a cleft overcomes hardships during childhood and adolescence, they face another serious obstacle: **the risk that the cleft anomaly could return** (recurrence) and affect his or her children.

The risk of recurrence varies from 3% to 15%, regarding to the type of cleft and sex of the affected. Also, approximately the same risk of recurrence exists for siblings born after the child with the cleft.

We know the precise figures of recurrence risk and can provide the family with them during genetic evaluation and counseling.

The fact that cleft lip and palate, and a cleft palate alone, occur in close relatives of the affected individuals more often than in the general population, have been known since Danish plastic surgeon Poul Fogh-Andersen published his study more than a half century ago.

	Recurrence risk in %			
Sex of proband and severity	in sib	IS	in chi	ildren
of the defect	brother	sister	son	daughter
MALE with unilateral cleft	2.33	1.35	4.91	2.27
FEMALE with unilateral cleft	4.17	4.41	4.55	3.03
MALE with bilateral cleft	3.26	3.13	11.54	4.88
FEMALE with bilateral cleft	15.78	7.14	17.24	7.69

Recurrence risk in nonsyndromic cleft lip with or without cleft palate ($CL\pm P$) in Caucasian based on a large study of families.

proband = patient (individual affected with cleft)

Tolarova and Cervenka, 1993



Are Orofacial Clefts Preventable?

The available research on the association between orofacial clefts and folic acid consumption highly suggests that a certain proportion of these anomalies can be prevented by periconceptional supplementation of Folic Acid and multivitamins.

It is assumed that the preventive approach will be especially successful in those cases in which environmental factors represent a substantial part of the etiological background.

Primary prevention, i.e., prevention of a birth defect before it develops in embryo or fetus, is applied either

- in the risk families where a baby with the anomaly has already been born prevention of *recurrences*
- or in the general population prevention of *occurrences*

You are most likely reading this pamphlet because you yourself or your close relative (your child or your sibling) had orofacial cleft.

Why are we so confident about cleft prevention? Because our studies on the prevention of cleft lip and palate clearly showed scientific evidence for it.

There are also studies by others before and after our research showing or suggesting that nonsyndromic cleft lip and palate are preventable.

Our first study was published

In 1995 two studies reported that mothers who took multivitamins with folic acid periconceptionally significantly decreased their risk for having a child with an orofacial cleft.

Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet 1995; 346:393-396



Tolarova MM, Harris JA. Reduced recurrence of orofacial clefts after periconceptional supplementation with high dose of folic acid and multivitamins. Teratology 1995; 51:71-78



Prevention

Historical Studies

Fifteen years after Poul Fogh-Andresen published the Danish study, plastic surgeons *Lyndon E. Peer, Beverly Douglas, Herbert Conway* and their colleagues in the United States conducted initial studies attempting to prevent recurrence of orofacial clefts based on knowledge of etiology of birth defects obtained from studies on experimental animals and humans. Vitamins, including folic acid were given to women at risk for having a child with a cleft to prevent recurrences.

It is interesting to note that studies to prevent recurrences of orofacial clefts actually started much earlier than today's well-known studies on the prevention of neural tube defects.

> "The health and physiologic development of a fetus depend integrally on the mother's nutritional status at its conception and her diet during pregnancy."

> > Warkany and Nelson, 1940

"Even granting that a healthy pregnant woman is receiving a good diet, it is probably not always true that she is necessarily getting enough vitamins to satisfy the demands of fetal organogenesis during the first trimester."

Beverly Douglas, 1958





Our Studies

In a large but non-randomized prospective interventional trial on a sample of the Czech population, Tolarova *(Tolarova and Harris, 1995)* showed that periconceptional supplementation with multivitamins and 10 mg of folic acid reduced the recurrence risk for cleft lip with or without cleft palate ($CL\pm P$) by about 65%.

• SUPPLEMENTED GROUP

N=221 mothers with a positive family history

- 133 previous child affected with CL or CLP
- 88 prospective mother or father affected with CL or CLP

NONSUPPLEMENTED GROUP

N=1,901 mothers with a positive family history 1,046 previous child affected with CL or CLP 855 prospective mother or father affected with CL or CLP

Protocol

- 1. Genetic evaluation and physicals proband and 1st-degree relatives
- 2. Risk of recurrence
- 3. Medical examination of prospective mothers
- 4. Gynecological examination of prospective mothers
- 5. Treatment
- 6. Optimal time of conception recommended
- 7. Living conditions considered
- 8. Periconceptional supplementation 2 months before + 3 months after conception
- 9. All mothers are seen every month
- 10. Newborns examined

Supplementation regimen

Multivitamin supplements were given as 3 tablets daily,

of which 1 tablet contains:

٠	Vitamin A	200 IU
•	Vitamin B1	1 mg
•	Vitamin B2	1 mg
٠	Vitamin B ₆	1 mg
•	Vitamin C	30 mg
•	Vitamin D ₃	100 IU
•	Vitamin E	2 mg
•	Nicotinamide	10 mg
•	Calcium Panthotenicum	1 mg

FOLIC ACID 10 mg (10,000 mcg) daily given in one tablet



Recurrence of clefts in supplemented and non-supplemented groups

(Tolarova and Harris, 1995)



What was found in the Czech study?

- Decrease of recurrences by 65.4% in supplemented pregnancies with previous child or parent affected with CL±P
- Decrease of recurrences by 82.6% in the subset of supplemented pregnancies with previous child or parent affected with unilateral CL±P
- No change of recurrences in the subgroup of supplemented pregnancies with previous girl or mother affected with bilateral CL±P
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Similarly, in a large population-based case-control study in the California population, Shaw *(Shaw et al. 1995)* showed that periconceptional use of multivitamins, which usually contain 0.4 mg or more of folic acid, reduced the occurrence risk for $CL\pm P$ by approximately 50%.

- data were derived from a population-based case-control study in California
- mothers of 731 children with a cleft (cases) and mothers of 734 children without birth defects (controls) were interviewed

Women who used multivitamins containing 0.4 mg or more folic acid periconceptionally had a 27%-50% reduction in risk for having a child with an orofacial cleft.

The highest reduction (50%) was found in the subgroup of isolated CL±P.

Reduced risk in other subgroups: CL±P multiple by 39% CP isolated by 27% CP multiple by 36%



(isolated = cleft only, multiple = cleft + another congenital anomaly)





Three Necessary Requirements

for healthy embryonic and fetal development

- 1. healthy mother
- 2. healthy lifestyle
- 3. healthy nutrition

Several Basic Rules

- Plan Your Pregnancy

You planned carefully when you decided to buy the house, car, etc. To have a baby, it is even more important to plan.

➡ Get Genetic Evaluation

There are several types of clefts, and a geneticist will specify the diagnosis. Based on the correct diagnosis and an analysis of your medical and pregnancy history, the best preventive approach can be chosen.

Learn About Prevention

The majority of clefts are caused by the interaction of genetic and environmental factors. A certain proportion of these clefts is preventable by nutritional changes and supplementation with multivitamins containing folic acid.





➡ Make Necessary Changes in Your Lifestyle

Our current lifestyle is often far from optimum. We are exposed to environmental pollution, stress, etc. However, if you are planning a baby, there are many changes you should make to decrease the risk for congenital anomalies caused by environmental factors

- Do not smoke
- Do not drink alcoholic beverages
- Exercise and increase outdoor activities
- Get enough sleep
- Find the best way to reduce stress
- Maintain healthy weight

See Your Primary Physician and ObGyn Specialist to Learn About Your Present Health Status

It is quite logical that only a healthy mother can assure a healthy embryonic and fetal development of the baby. However, if you have a medical problem that is known before you become pregnant, in most cases, it can be safely managed during pregnancy or treated before you become pregnant (diabetes is one example of disease found associated with increased risks for congenital anomalies).







Focus on Your Nutrition

In general, your diet should be well balanced to secure that you are getting enough necessary nutrients.

- Focus on variety, nutrient density, and amount¹
- Choose unprocessed food as often as possible
- Choose vegetables and fruits
- Add nuts and seeds
- Reduce meat and processed meat products
- Limit calories from added sugar and saturated fat
- Reduce sodium intake¹
- Shift to healthier food and beverage choices¹
- Get enough folic acid in your diet

Especially if you are at risk for having a baby with cleft lip and palate, you need enough folic acid, Vitamin B_{6} , Vitamin B_{12} , and Zinc to secure normal prenatal development.

See the chart for a list of the best natural sources of folates.

• Take Supplements

Studies show that a large proportion of the American population is not getting enough folic acid from their diet. Such a deficiency could put a fragile developing human being at significant risk for congenital anomalies.

At present, the recommendation for pregnant women is 400 mcg a day^2 . Many, prenatal multivitamins contain 800 mcg. You should start to take them the moment you decide to plan a pregnancy.

^{1 -} https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf

^{2 -} CDC recommendation - https://www.cdc.gov/ncbddd/birthdefects/prevention.html



About Folic Acid

Overview

In 1941, a substance extracted from spinach leaves and named folic acid from the Latin word "folium" for leaf was found to be effective in treating anemia.

Folate and folic acid are different terms for the same B9 vitamin. While these two terms are often used interchangeably, we make some distinctions between them. Folate is the form found naturally in foods. Folic acid is not found in natural food sources. Folic acid is the synthetic form that is used in vitamin supplements and added to fortified foods.

Synthetic folic acid is about twice as absorbable as naturally occurring food folate. The folic acid in the diet is converted to its biologically active form in the body with the help of vitamin B_{12} , niacin, and vitamin C. The folic acid is absorbed from the small intestine, and small amounts are stored in the liver and other tissues. Excess is excreted in the urine.

Functions

Folic acid's main function is to maintain the cells' genetic code and regulate cell division and the transfer of inherited traits from one cell to another.

It is essential for the normal growth and maintenance of all cells. In other words, folic acid participates in several metabolic processes in the body, the most important being the synthesis of DNA. That is why it is very important for a woman to have enough folic acid in her body both before and during pregnancy.





Deficiency

Among folic acid deficiency symptoms are macrocytic (megaloblastic) anemia, poor growth, digestive disorders, impaired nutrient absorption and malnutrition, diarrhea, loss of appetite, weight loss, weakness, apathy, sore tongue, headaches, heart palpitations, irritability, and behavioral disorders.

However, a higher level than the one sufficient for adults and children is needed in the beginning of pregnancy. When deficiency occurs it may lead to disturbance for normal development of embryo and a congenital anomaly in the newborn.

Sources in the Diet

Unlike vitamin B₁₂, which is present only in animal-based food, folate is ubiquitous, being present in nearly all natural foods.

Again, unlike vitamin B_{12} , folate is highly susceptible to oxidative destruction; 50 to 95% of the folate content of foods may be destroyed by protracted cooking or other processing such as canning, and all folate is lost from refined foods.

The vitamin is easily lost when foods are improperly stored for too long or at too warm a temperature or are overcooked or reheated.

The vitamin is also lost when the cooking water is discarded.

The best dietary sources of folate are brewer's (nutritional) yeast, dark green leafy vegetables, and liver. Orange juice, avocado, beets, and broccoli are also good sources.





Since 1998 cereal grain products are fortified with folic acid (140mcg per 100grams) and labeled enriched.

However, women capable of becoming pregnant who eat a healthy diet still need to take a vitamin supplement, eat daily a breakfast cereal containing 100% of the daily value of folic acid or increase their consumption of foods fortified with folic acid to achieve the recommended amount of folic acid for the prevention of birth defects.

Why women at childbearing age should take folic acid in supplements.

The small amount of folic acid stored in the liver is not adequate to meet the additional needs imposed by pregnancy, stress, lactation, ingestion of certain medications, or alcohol.

Folic acid may help reduce the risk of having a baby with certain birth defects of brain and spinal cord and other birth defects.

Recent findings suggest that folic acid can prevent certain types of cancer and cardiovascular atherosclerosis in adults.

It is most important to have enough folic acid in your system right before and early in pregnancy.

So, all women capable of becoming pregnant - not just those planning a pregnancy - should consume enough folic acid every day because half of all pregnancies in the United States are unplanned.





There are three ways women can get enough folic acid. They can choose to:

- 1. Take a vitamin supplement containing 400 micrograms of folic acid daily.
- 2. Eat a fortified breakfast cereal daily which contains 100% of the recommended daily amount of folic acid (400 micrograms).
- 3. Increase consumption of foods fortified with folic acid (e.g., "enriched" cereal, bread, rice, pasta, and other grain products) in addition to consuming food folate from a varied diet (e.g., orange juice and green vegetables).





Recommended Dietary Allowances (RDAs)¹

- 1 mcg DFE = 1 mcg food folate
- 1 mcg DFE = 0.6 mcg folic acid from fortified foods or dietary supplements consumed with foods
- 1 mcg DFE = 0.5 mcg folic acid from dietary supplements taken on an empty stomach

Age and sex group	Dietary Folate Equivalent mcg DFE	B6 (mg)	В ₁₂ (mcg)	Zinc (mg)
INFANTS				
0- 6 months	65	0.1	0.4	2
6 months – 1 year	80	0.3	0.5	3
CHILDREN				
1-3 years	150	0.5	0.9	3
4-8 years	200	0.6	1.2	5
9-13 years	300	1.0	1.8	8
Males 14-18 years	400	1.3	2.4	11
Females 14-18 years	400	1.2	2.4	9
ADULTS				
Males 19+ years	400	1.3	2.4	11
Females 19+ years	400	1.3	2.4	8
Females 19+ years	400	1.9	2.6	11
Pregnant	600			15
Lactating, 1 st 6 months	500	2.0	2.8	12
Lactating, 2 nd 6 months	500	2.0	2.8	12

¹ Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998. <u>https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/</u>





Folic Acid and Vitamin B₁₂ in Food

Food	Amount	Folic Acid (mcg)
Brewer's (nutritional) yeast	1 Tbsp	313
Liver, beef	3 ounces	115
Spinach, raw	1 cup	58
Spinach, cooked	¹ / ₂ cup	131
Orange juice	6 ounces	35
Cereals, fortified (see label)	¹ / ₂ cup	100
Lettuce, romaine	1 cup	64
Beets, cooked	¹ / ₂ cup	
Avocado	1/2 medium	59
Broccoli, cooked	¹ / ₂ cup	52
Wheatgerm	2 Tbsp	40
Beans, red-cooked	¹ /2 cup	
Banana	1 medium	24
Brussels sprout, cooked	¹ / ₂ cup	78
Bread, white	1 slice	50

The Folic Acid Content of Selected Foods Sources¹

The Vitamin B₁₂ Content of Selected Foods Sources

Food	Amount	Vitamin B ₁₂ (mcg)
Liver, beef	3 ounces	68.0
Clams, canned	1/2 cup	84.1
Oysters, canned	3 ¹ / ₂ ounces	18.0
Tuna	3 ounces	2.5
Yogurt	1 cup	1.1
Milk, non-fat	1 cup	1.2
Halibut	3 ounces	0.85
Egg	1 large	0.6
Chicken	3 ounces	0.3
Cheese, Cheddar	1 ounce	0.9



¹U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019. <u>fdc.nal.usda.gov.</u>





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