

# FOLIC ACID IN PREGNANCY

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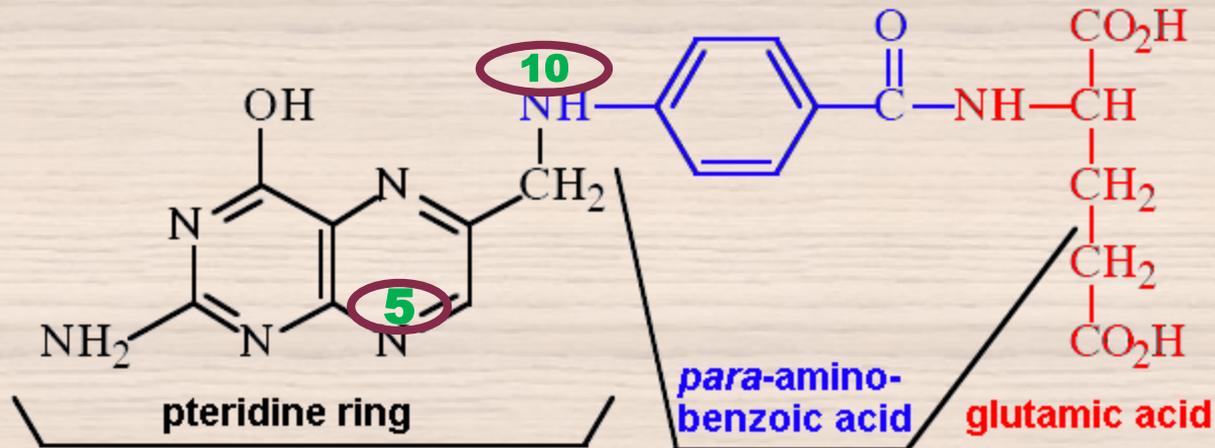


# Chemistry

- The word folic acid is derived from latin word Folium means leaf & it is also isolated from the leafy vegetable spinach
- Folic acid mainly consists of **three components**
- **Pteridine ring**
- **PABA (p-amino benzoic acid)**
- **Glutamic acid residue (1 to 7 residues)**
- Hence it is known as **Pteroyl-glutamic acid**

# ACTIVE FORM

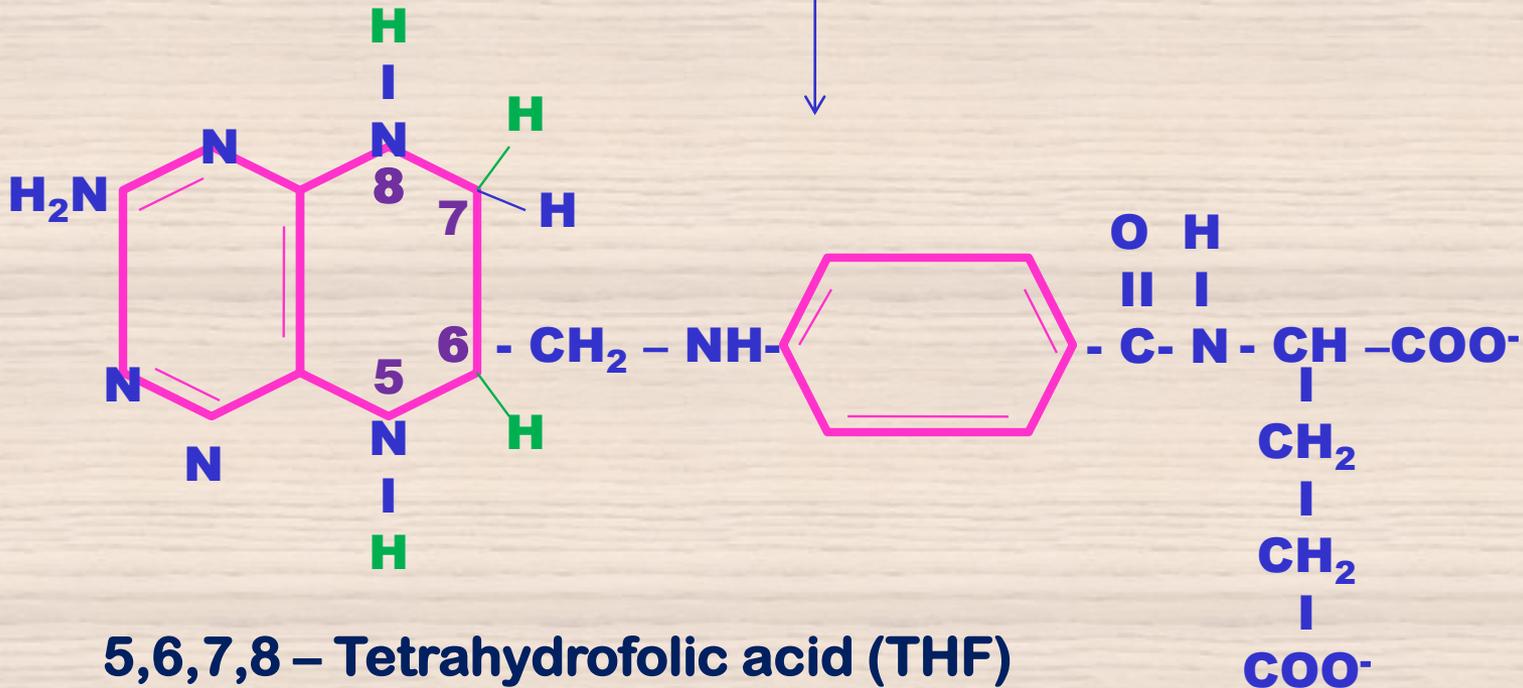
- Tetrahydrofolate (THF or FH<sub>4</sub>) is the active form of folic acid



# Folic Acid



Dihydrofolate  
reductase



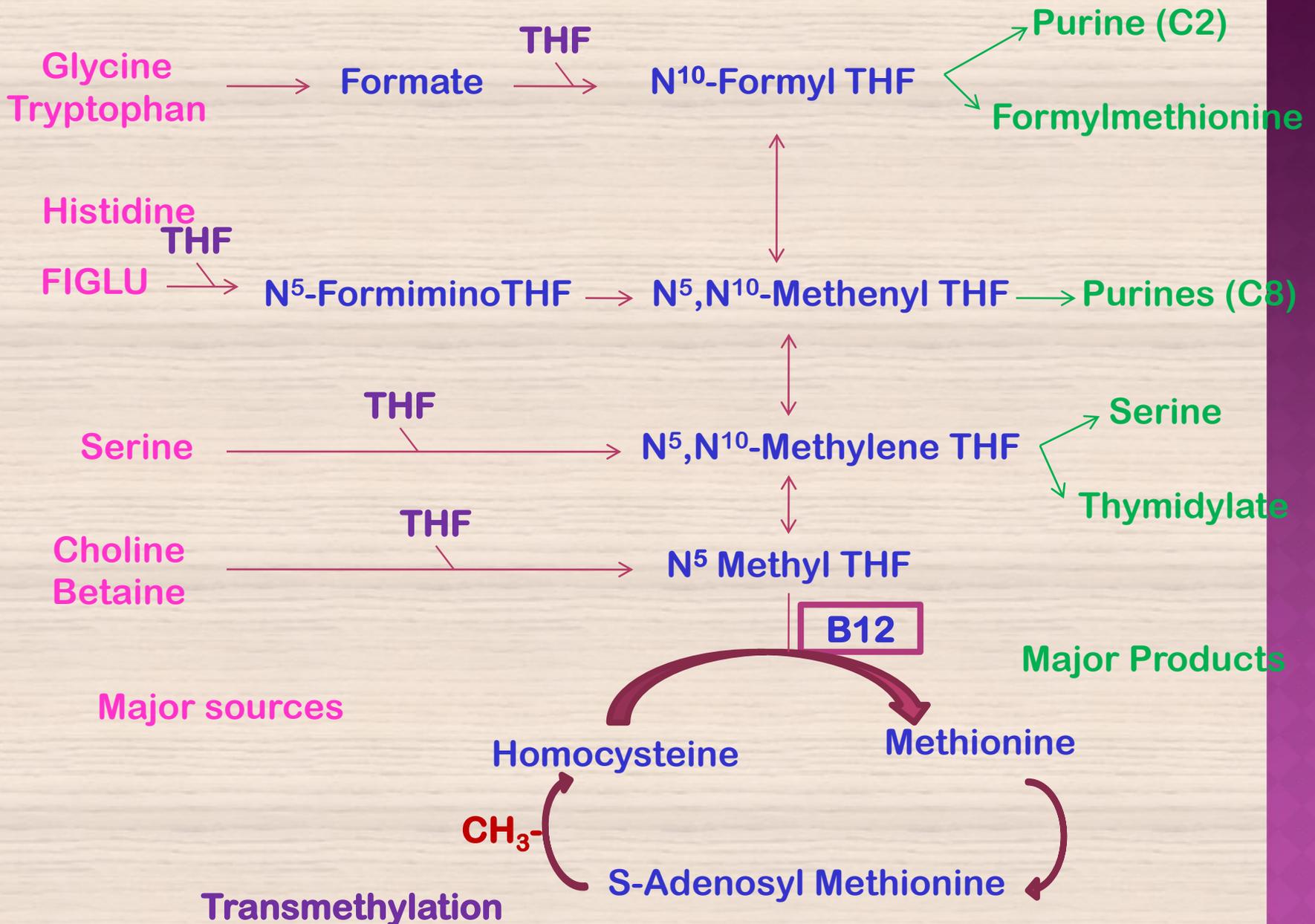
# METABOLISM

- ◎ **Absorption:**
- ◎ **Formation of monoglutamate form:**
- ◎ **Most of the dietary folic acid exists as polyglutamate with 3-7 glutamate residues**
- ◎ **It is not absorbed in the intestine**
- ◎ **The glutamate side chains are cleaved by the enzyme **folate conjugase** or **poly/polyglutamate hydrolase****

- ◉ Only monoglutamyl form of folic acid is absorbed from the intestine
- ◉ The enzyme folate conjugase is present in duodenum & jejunum
- ◉ Mucosal uptake & metabolism in mucosal cell
- ◉ Folate monoglutamate is taken up by the mucosal cell
- ◉ In the mucosal cell, folate monoglutamate is reduced to tetrahydrofolate & methylated to form N<sup>5</sup> methyl tetrahydrofolate (in circulation)

- ◉ N<sup>5</sup> methyl tetrahydrofolate enters the circulation
- ◉ **Storage:**
- ◉ Inside the cells, tetrahydrofolates are found as polyglutamates (with 5-6 amino acid residues)
- ◉ Which are biologically most potent
- ◉ Polyglutamate is the storage form of folic acid
- ◉ It is mainly stored in the liver (10-20 mg)

# One Carbon Metabolism



**Ácido Fólico**  
**Folic**  
**Acid**

**Every Body Needs It**

**Folic Acid Training**  
**Contra Costa FIMR Program**

# Take Home Message

- All women should be informed of folic acid.
- All women capable of becoming pregnant could have an **NTD-affected** pregnancy.
- All women should consume **400 micrograms of folic acid daily** in addition to foods high in folate such as fruits and vegetables
- All women should be physically **active for at least 30 minutes a day**

# What is Folic Acid?

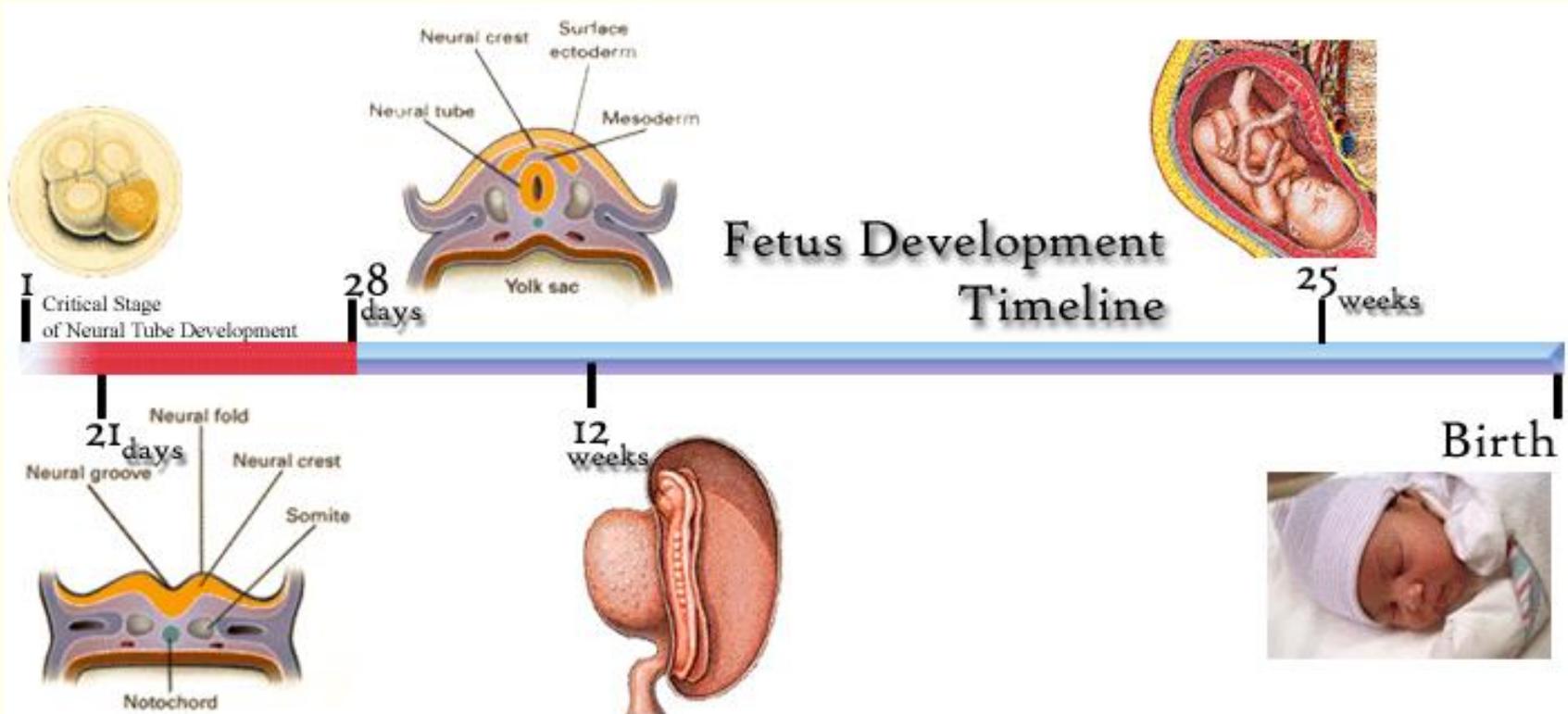
- B vitamin
- Involved in DNA synthesis
- Role during pregnancy
  - Prevent certain birth defects of the brain and spine called neural tube defects (**NTDs**)
  - Supports growth of the placenta and fetus
- Necessary for overall good health

# How do **NTDs** Occur?

- Neural tube starts as a ribbon of tissue in embryo.
- Folds in on itself and forms a tube within first month of pregnancy
- Ultimately forms the spinal cord, spine, brain and skull

*NTDs result when the neural tube doesn't properly close.*

# Neural Tube Development



# Spina Bifida

- Baby's spine is not completely formed.
- May cause paralysis of the lower body, bladder and bowel control problems, and learning disabilities.
- **Affects approximately one in every 1,000 newborns**
- Average lifetime cost for child with spina bifida is in the hundreds of thousands.



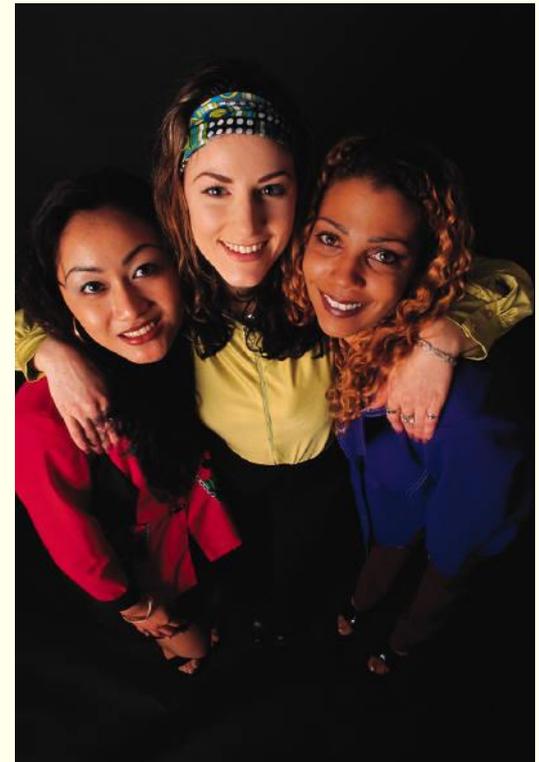
# Anencephaly

- Top part of the brain and skull doesn't completely form
- Affected pregnancies either result in miscarriage, stillbirth, or death shortly after birth



# Who is at risk for NTDs?

- All women capable of becoming pregnant
- 95% of NTDs occur in women with no family history of NTDs
- There are some known risk factors



# Some Risk Factors for NTDs

- Previous NTD-affected pregnancy
- Maternal insulin-dependent diabetes
- Obesity
- Race/ethnicity
- Some anti-seizure medications
- High temperatures early in pregnancy (e.g., prolonged fevers, hot tub use)
- Lower socio-economic status

# The Role of Folic Acid

- Can **reduce** the risk of **NTDs** by **50 to 70** percent

*HOWEVER...*

- Folic acid must be consumed before and early in pregnancy to lower your chance of NTDs

# The Challenge

- **NTDs** happen in the **first month** of pregnancy – before most women know they are pregnant.
- Half of all pregnancies in the US are not planned.



*Be prepared!*

# Recommended Daily Value of Folic Acid

Non-pregnant women and men aged 14 yrs and older	400 mcg
Pregnant women* and women planning a pregnancy	600 mcg
Breastfeeding women	500 mcg
9-13 years (boys and girls)	300 mcg
4-8 years (boys and girls)	200 mcg
1-3 years (boys and girls)	150 mcg

\* Women with previous NTD-affected pregnancy should talk to their doctor

# Is Diet Enough?

- Eating a healthy diet rich in **fruits** and **vegetables** is important!
- Most people get some folic acid through their diet, but you need a source of 400 mcg of folic acid to be sure you get enough.

***Two thirds** of women in the U.S. do not get enough folic acid.*

# Sources of Folic Acid

1. Multivitamins and fortified cereals



2. Other fortified foods

3. Foods with naturally occurring folate



# Folic Acid vs. Folate

- The natural form of folic acid found in foods is called folate.
- Folic acid is the found in vitamins and fortified foods.
- Folic acid is better absorbed by the body than folate.
- Once absorbed by your body, folic acid is converted into folate.

## Foods With Folic Acid

- Dark green leafy vegetables, like spinach
- Broccoli, asparagus, green peas and okra
- Orange juice
- Papaya
- Beans, lentils and black-eyed peas
- Soybeans and tofu
- Peanut butter
- Fortified foods: Cereal, rice, pasta, tortillas, grits



*Be sure to eat 5 servings of fruits & vegetables such as these every day!*

# Can You Get Too Much Folic Acid?

- No known level at which it is toxic, even in high amounts
- Even if you eat fruits and vegetables containing folic acid, eat a bowl of cereal and take a multivitamin with folic acid in one day, you would not have a problem with too much folic acid

## Higher-dose folic acid

- If you have a higher chance of your pregnancy being affected by neural tube defects, you will be advised to take a **higher dose of folic acid (5 milligrams)**. You will be advised to take this each day until you're 12 weeks pregnant.

# Higher-dose folic acid

You may have a higher chance if:

- you or the baby's biological father have a neural tube defect
- you or the baby's biological father have a family history of neural tube defects
- you have had a previous pregnancy affected by a neural tube defect
- you have diabetes
- you take anti-epilepsy medicine
- you take anti-retroviral medicine for HIV
- If any of this applies to you, talk to a GP. They can prescribe a higher dose of folic acid.

# Higher-dose folic acid

- ✓ epilepsy
- ✓ type 2 diabetes
- ✓ rheumatoid arthritis
- ✓ lupus
- ✓ inflammatory bowel disease (IBD)
- ✓ celiac disease
- ✓ People undergoing kidney dialysis may also wish to avoid taking folic acid.

# Recommendations

- Consume **400 mcg** of folic acid daily by:
  - Taking a multivitamin with 400 mcg of folic acid or eating cereal with 400 mcg per serving, and
  - Eat a diet of fruits and vegetables rich in folate in addition to foods fortified with folic acid
- Be physically active for **30 minutes every day**
- Read your food labels for folic acid content

# Sample food label

- Look for “Folic Acid” or “Folate” in the left column
- Check value in the right column – this number is the percent of your recommended daily value (100% = 400 mcg)

<b>Nutrition Facts</b>		
Serving Size 1 cup (55 g)		
Servings Per Container About 12		
Amount Per Serving	(Name of cereal)	with 1/2 cup skim milk
Calories	170	210
Calories from Fat	10	10
<b>% Daily Value**</b>		
Total Fat 1 g*	1%	2%
Saturated Fat 0g	0%	0%
Polyunsaturated Fat 0g		
Monounsaturated Fat 0g		
<b>Cholesterol 0mg</b>	<b>0%</b>	<b>1%</b>
<b>Sodium 240 mg</b>	<b>10%</b>	<b>13%</b>
<b>Potassium 360mg</b>	<b>10%</b>	<b>16%</b>
<b>Total Carbohydrate 41g</b>	<b>14%</b>	<b>16%</b>
Dietary Fiber 5g	20%	20%
Sugars 20g		
Other Carbohydrate 16g		
<b>Protein 4g</b>		
Vitamin A	10%	15%
Vitamin C	0%	0%
Calcium	100%	110%
Iron	100%	100%
Vitamin D	10%	25%
Vitamin E	100%	100%
Thiamin	100%	100%
Riboflavin	100%	110%
Niacin	100%	100%
Vitamin B6	100%	100%
<b>Folic Acid</b>	<b>100%</b>	<b>100%</b>
Vitamin B12	100%	110%
Pantothenic Acid	100%	100%
Phosphorus	10%	25%
Magnesium	10%	10%
Zinc	100%	100%
Copper	8%	8%

# Barriers to Folic Acid Absorption or Use

- Alcohol
- Tobacco
- Aspirin, ibuprofen, naprosyn and acetaminophen
- Antacids & anti-ulcer medications
- Some antiseizure medications
- Some anticancer drugs
- Some antibiotics/antibacterials
- Oral hypoglycemic agents

# Other Benefits of Folic Acid

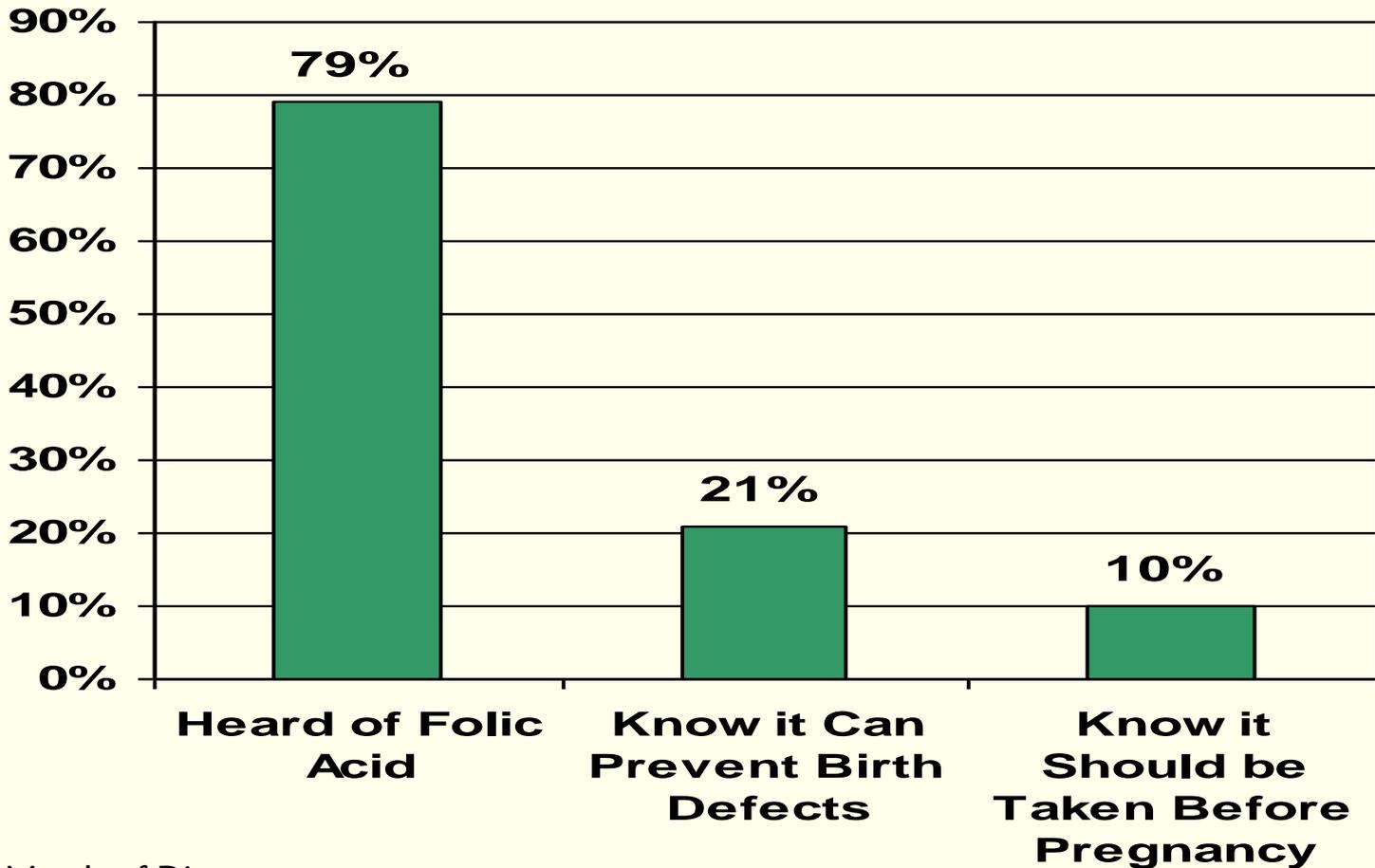
- Benefits extend beyond preventing NTDs
- May prevent:
  - Cleft lip and palate
  - Strokes
  - Heart disease
  - Colon cancer
  - Cervical cancer

# New Areas of Research

- Scientists are examining the links between low levels of folic acid and:
  - Alzheimer's Disease
  - Depression
  - Low sperm count
  - decreased sperm density

# Your Role in Folic Acid Education

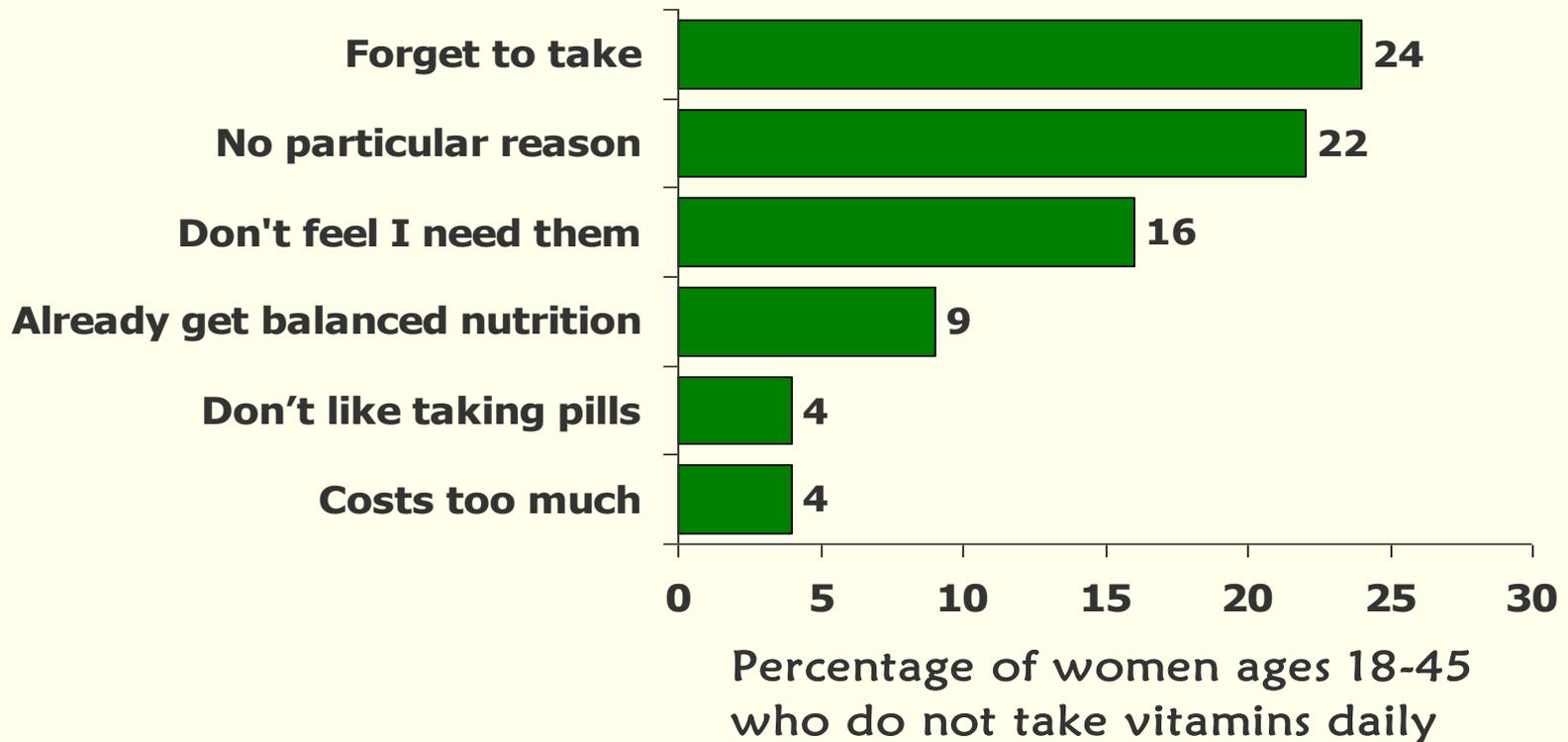
# Women's Knowledge of Folic Acid (March of Dimes Survey, 2003)



Source: March of Dimes.

# Top Reasons Why Women Do Not Take a Multivitamin Daily

(March of Dimes Survey, 2003)



# You are important!

- $<1/3$  of women of childbearing age take a multivitamin with folic acid.
- One third of these women said they would be more likely to do so if a doctor or other health care worker recommended it.

# What you can do

- Talk to your clients about the importance of folic acid
- Encourage all clients to eat a healthy diet rich in fruits and vegetables and to be physically active for 30 minutes a day
- **PRENATAL WOMEN:** Encourage clients to continue their prenatal vitamins throughout their pregnancy
- **POSTPARTUM WOMEN:** Encourage clients to switch to a regular daily multivitamins after finishing their prenatal vitamins

# DIETARY SOURCES

- ⦿ Rich sources are green leafy vegetables such as spinach, cauliflower
- ⦿ Poor sources are liver, kidney, milk, fruits



# RDA

Men	-100 µg/day
Women	-100 µg/day
Pregnancy	-400 µg/day
Lactation	-150 µg/day

## DEFICIENCY

- ⦿ Dietary deficiency is the most common cause of folic acid
- ⦿ Dietary deficiencies are caused by
- ⦿ **Inadequate intake** seen in alcoholics
- ⦿ **Overcooking of food** resulting in loss of folic acid activity
- ⦿ **Impaired absorption** due to small intestinal diseases,
- ⦿ **Drugs interfere with folic acid absorption-sulfamethaxazole**

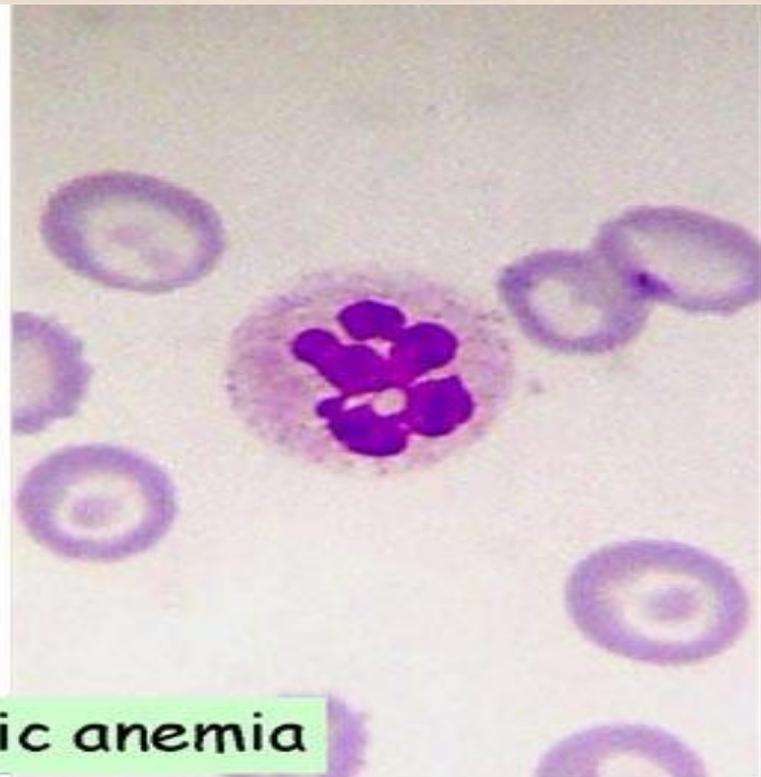
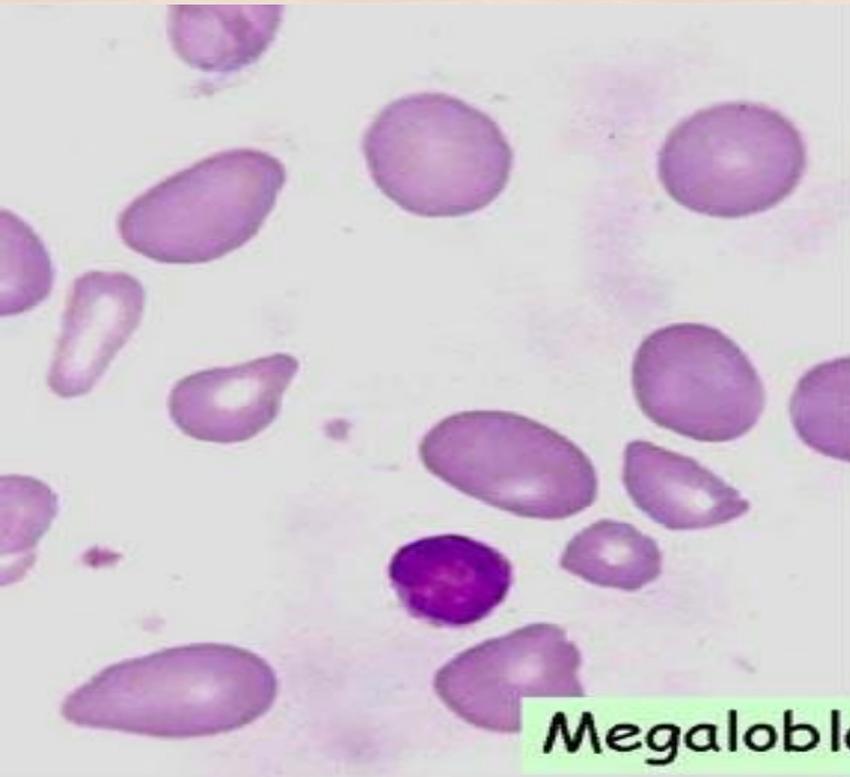
- ⦿ Increased demand of folic acid seen in pregnancy
- ⦿ Hemolytic anemia
- ⦿ Hence folic acid preparations are prescribed in pregnancy & hemolytic anemia
- ⦿ Other causes
- ⦿ Loss of folic acid seen in patients undergoing dialysis
- ⦿ Impaired synthesis of active form seen in patients receiving folic acid antagonists such as methotrexate

# CLINICAL FEATURES

- ◉ **Megaloblastic anemia** characterized by hyperchromic macrocytic anemia (due to maturation blocked)
- ◉ Megaloblastic changes are seen in bone marrow & mucosa
- ◉ Patients look pale
- ◉ **Glossitis**

# LABORATORY FINDINGS

- ⦿ Peripheral smear shows **macrocytic hyperchromic anemia**
- ⦿ Hypersegmentation of neutrophils is **common**



Megaloblastic anemia

- ⦿ Bone marrow shows megaloblastic changes characterized
- ⦿ abnormally large size of erythroid cells with cytoplasmic maturation
- ⦿ but impaired nuclear maturation due to defective DNA synthesis
- ⦿ Defective red cell production

## BIOCHEMICAL FINDINGS

- ⦿ Low plasma folic acid levels (<3ng/ml)
- ⦿ Low red cell folic acid levels (<150 ng/ml)
- ⦿ Normal plasma Vitamin B12 levels
- ⦿ Increased plasma LDH levels

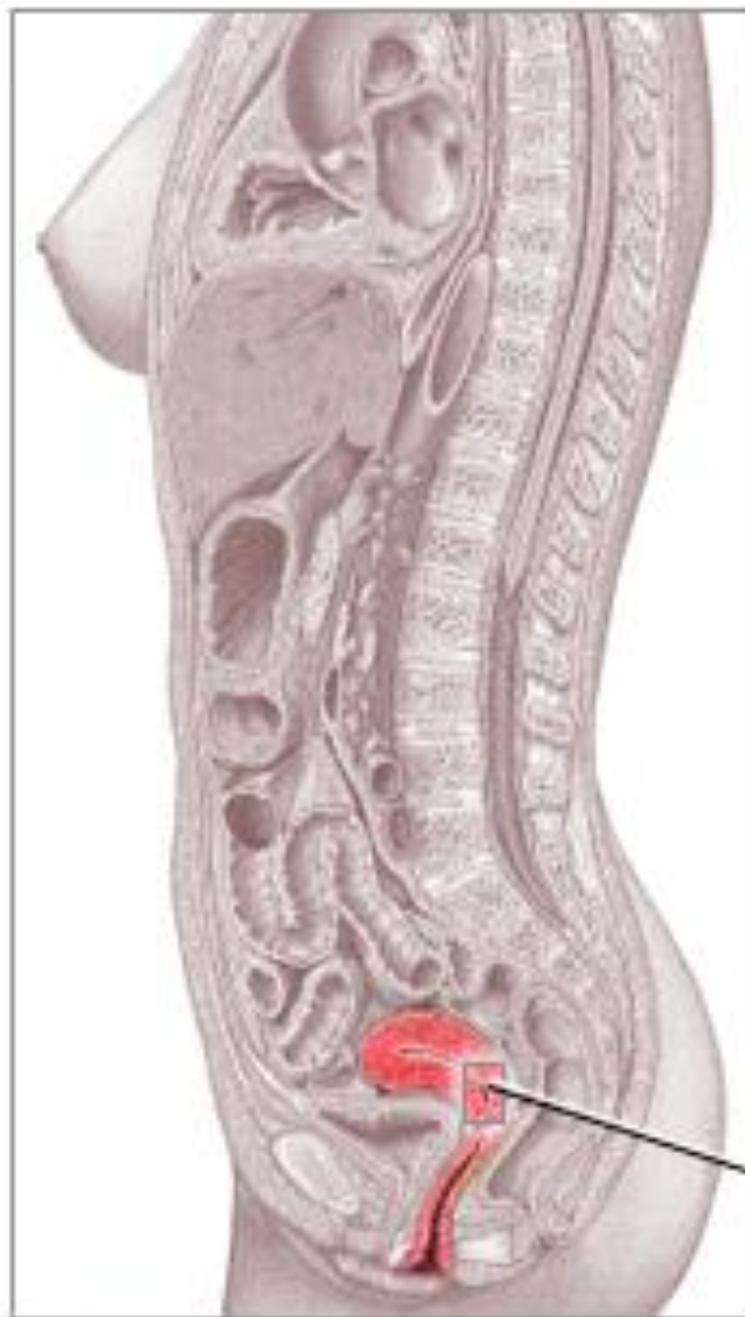
○ **FIGLU excretion test:-**

- Folic acid deficiency is associated with increased excretion of formiminoglutamate (FIGLU) in urine
- Due to impaired conversion of FIGLU to glutamate in a reaction requiring  $\text{FH}_4$



# FOLIC ACID DEFICIENCY & NEURAL TUBE DEFECTS

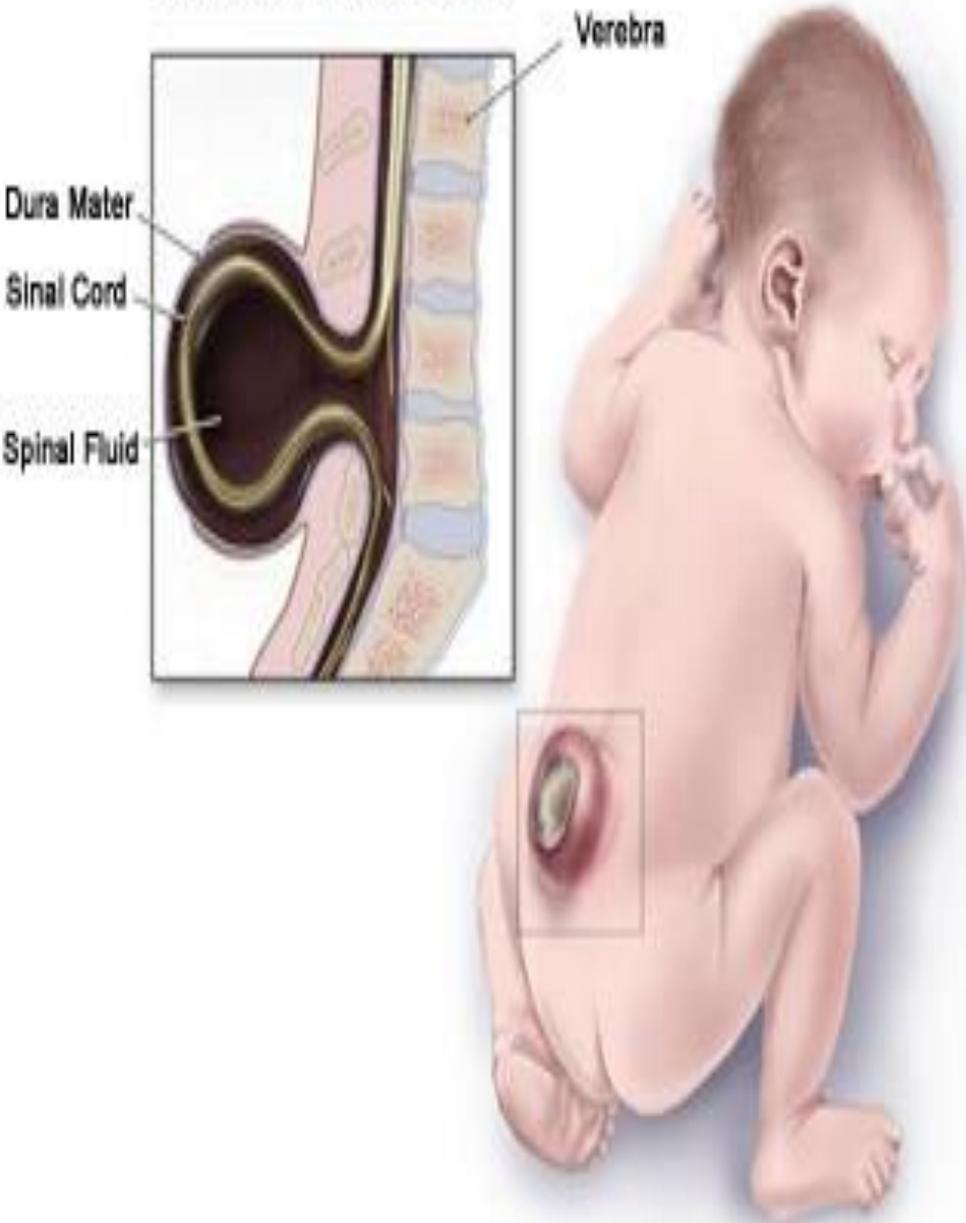
- ◉ Folic acid supplementation during pregnancy helps to prevent neural tube defects
- ◉ Mainly involved in brain & spinal cord
- ◉ Science, folic acid involved in nucleic acid & amino acid metabolism
- ◉ Deficiency results in impaired & aberrant neural development



Seven week  
old fetus

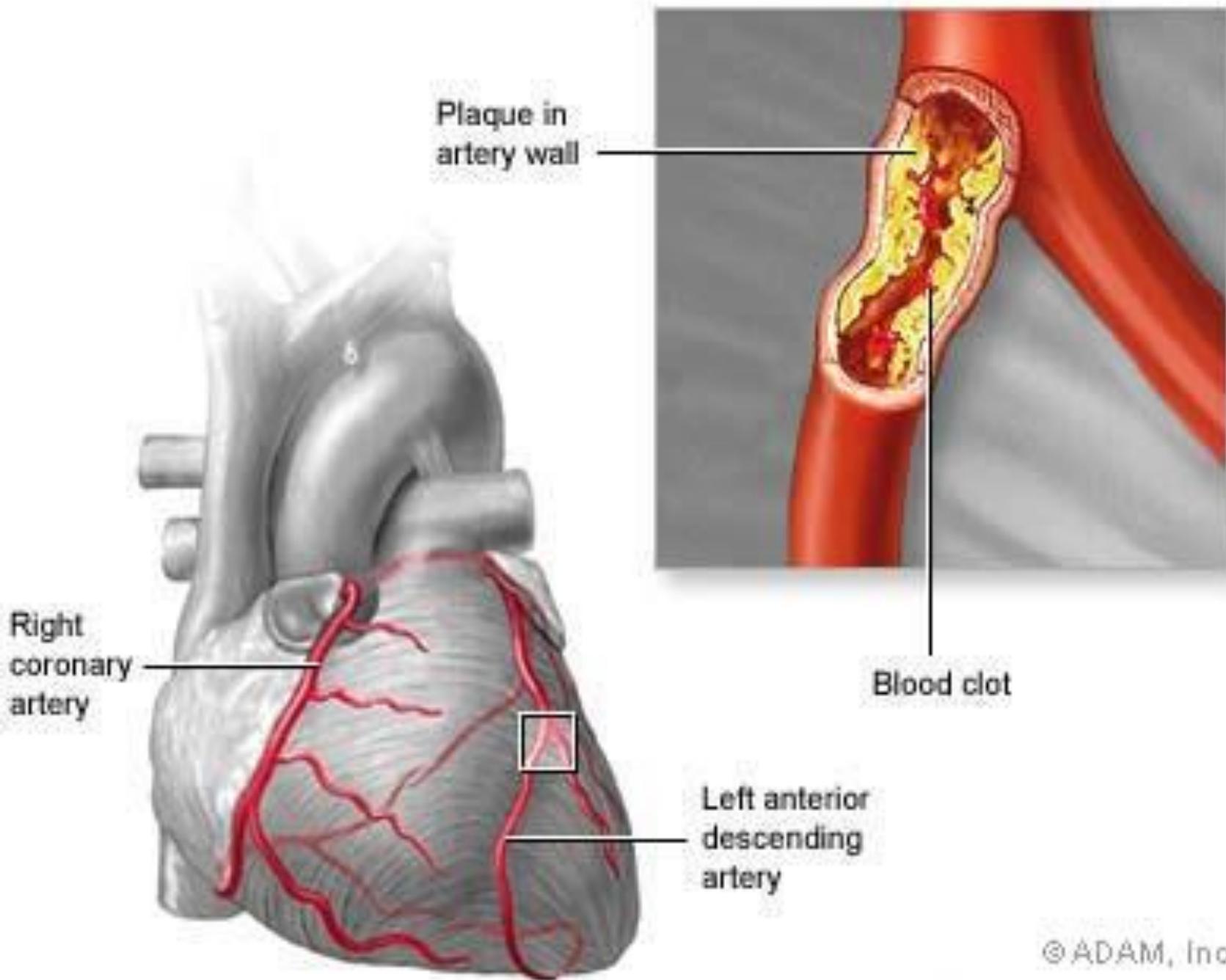
Uterus

# Spina Bifida (Open Defect)



# FOLIC ACID DEFICIENCY & HOMOCYSTEINEMIA

- ◉ Homocysteine is a risk factor for CHD
- ◉ Folic acid is required for conversion of homocysteine to methionine
- ◉ Deficiency is associated with
  - ◉ increased plasma levels of Homocysteine
  - ◉ Folic acid supplementation decreases plasma homocysteine levels
- ◉ Homocysteine levels are also increased in Vitamin B12 & Pyridoxine deficiency



# FOLIC ACID ANTAGONISTS

- ◉ Aminopterin & Amethopterin (methotrexate) competitively inhibit the enzyme **dihydrofolate reductase** in humans
- ◉ It impairs the formation of **active form of tetrahydrofolate from dihydrofolate**
- ◉ **Significance:-**
- ◉ During the conversion of deoxyuridylate to deoxythymidylate, dihydrofolate is formed, utilizes  $N^{5,10}$  methylene FH<sub>4</sub>

- ◉ Deoxythymidylate is required for DNA synthesis
- ◉ Folic acid antagonists will block DNA synthesis & inhibit cell division
- ◉ **Clinical uses:-**
- ◉ Aminopterin & Amethopterin (methotrexate) inhibit DNA synthesis in cancer cells
- ◉ Used in treatment of cancer
- ◉ Particularly leukemia & choriocarcinoma

# TRIMETHOPRIM

- ◉ It is a folic acid antagonist & it inhibits the bacterial **dihydrofolate reductase**
- ◉ Thus impairs the deoxythymidylate synthesis **leading to decreased synthesis of DNA**
- ◉ It is mainly used in bacterial infections