

**Folathaltige
orale
Kontrazeptiva-**

**Ein neues
Konzept**

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No conflict of
interest

Pregnancy and childbirth have never been as safe as today

Etiologies of perinatal morbidity and mortality

- **Premature delivery**

- Incidence - 6-10%
- ca. 70% of perinatal mortality
 - 50% of cerebral palsy

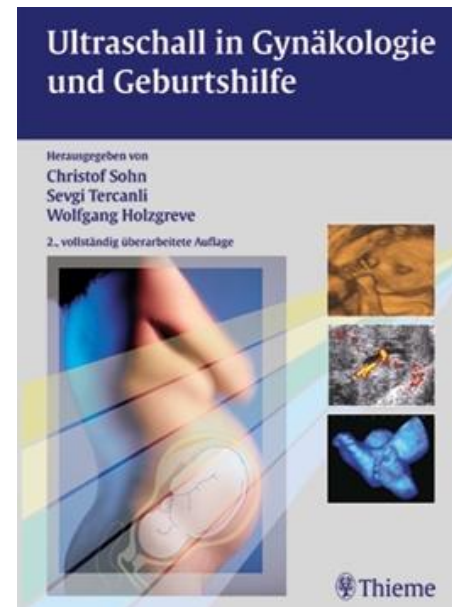


- **Intrauterine Growth restriction**

- Incidence - ca. 10%

- **Congenital anomalies**

Incidence - ca. 20%



Background philosophy: pregnancies are planned

- Pregnancy is a special time of life.
-
- Period of excitement and expectation
 - Uncertainties and desire to do the best for the baby
 - Termination of wanted pregnancies are to be avoided

Can the supplementation of folates and/or multivitamins provide a real prevention ?





Introduction of a new concept:

Using oral contraceptives to protect pregnancies

A modern oral contraceptive

is very reliable,

has no negative effect on blood

pressure, lipid or carbohydrate

metabolism etc.

...but OCs are taken in order

NOT to become pregnant! ?!?



Congenital anomalies- “Birth defects”

- **Definition:** an abnormality of structure, function or body metabolism present at birth that results in physical or mental disability, or is fatal.
- There are more than 4000 known types of birth defects.
- Birth defects are the leading cause of death in the first year of life.

Congenital anomalies are the leading cause of infant mortality

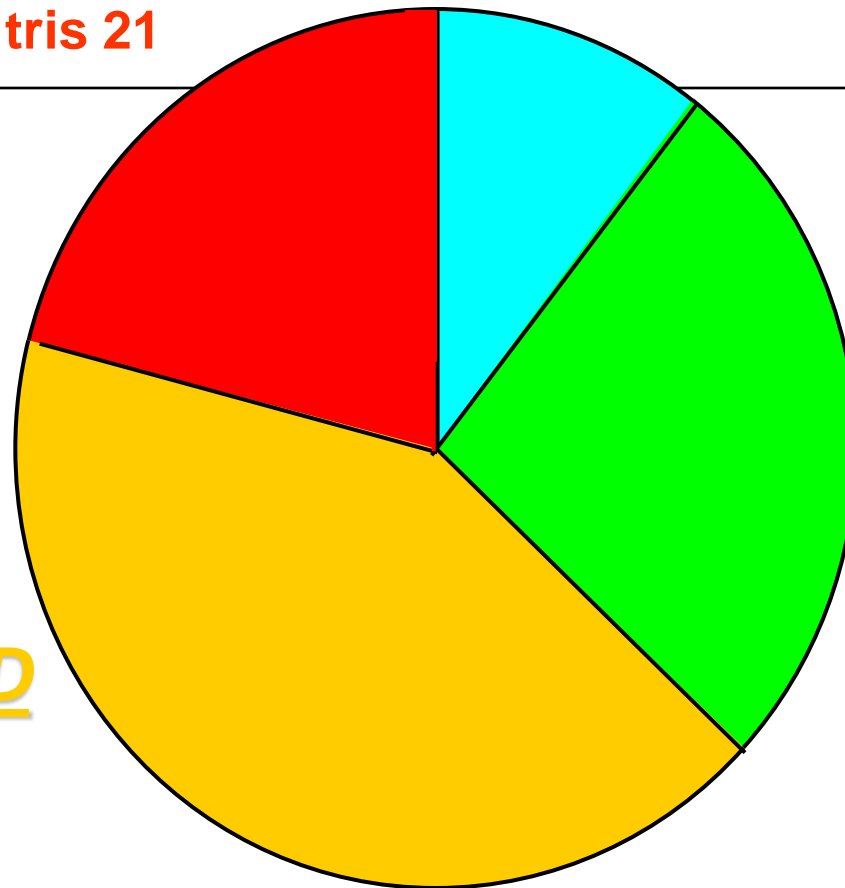
	Incidence	Mortality rate (per 100,000 live births)	Percent of all infant deaths
Congenital anomalies	3% ¹	134.6 ²	20%²
Premature delivery	13% ²	113.5 ²	17% ²
Low birth weight	8% ²		
Sudden infant death syndrome	N/A	54.0	8%

¹Canfield et al. Birth Defects Res A Clin Mol Teratol 2006;76:747-56;

²Mathews & MacDorman. Natl Vital Stat Rep 2008;57:1-32

Single gene diseases

Aneuploidies, esp. tris 21

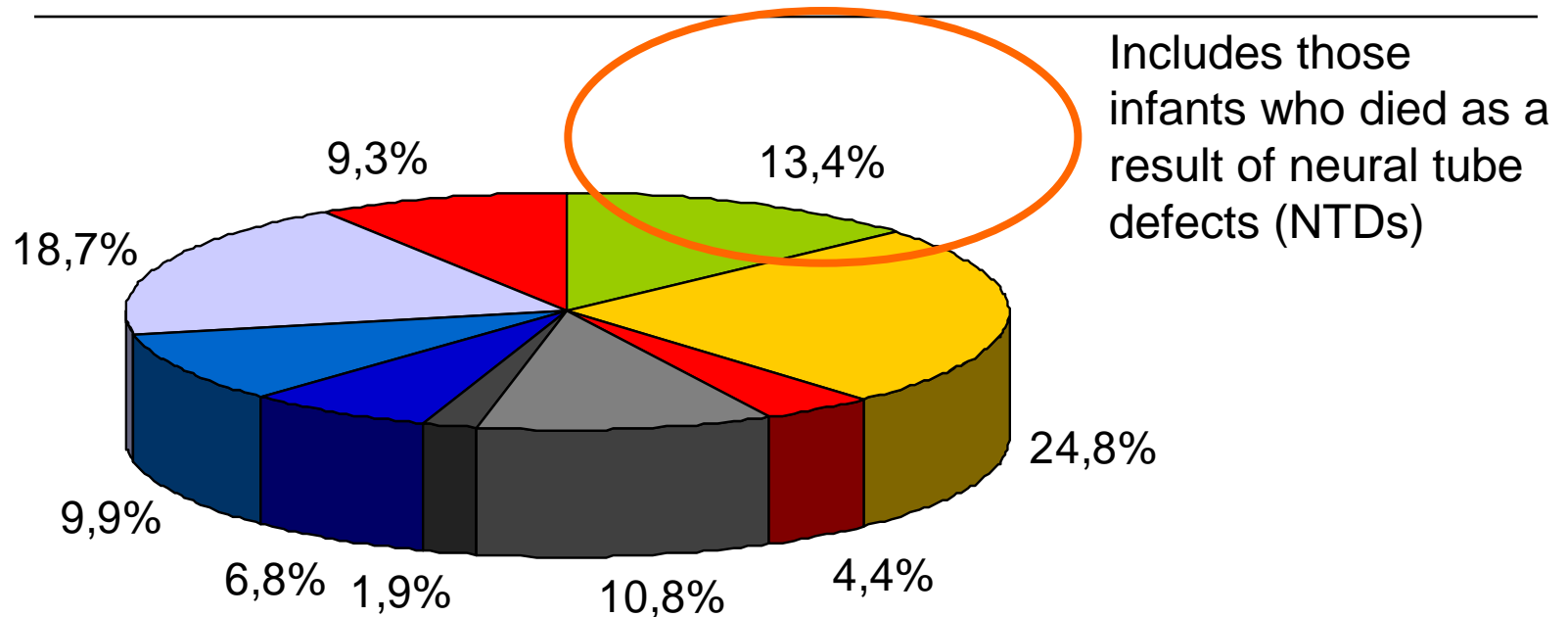


Heart defects

*Other structural
Defects, esp. NTD*

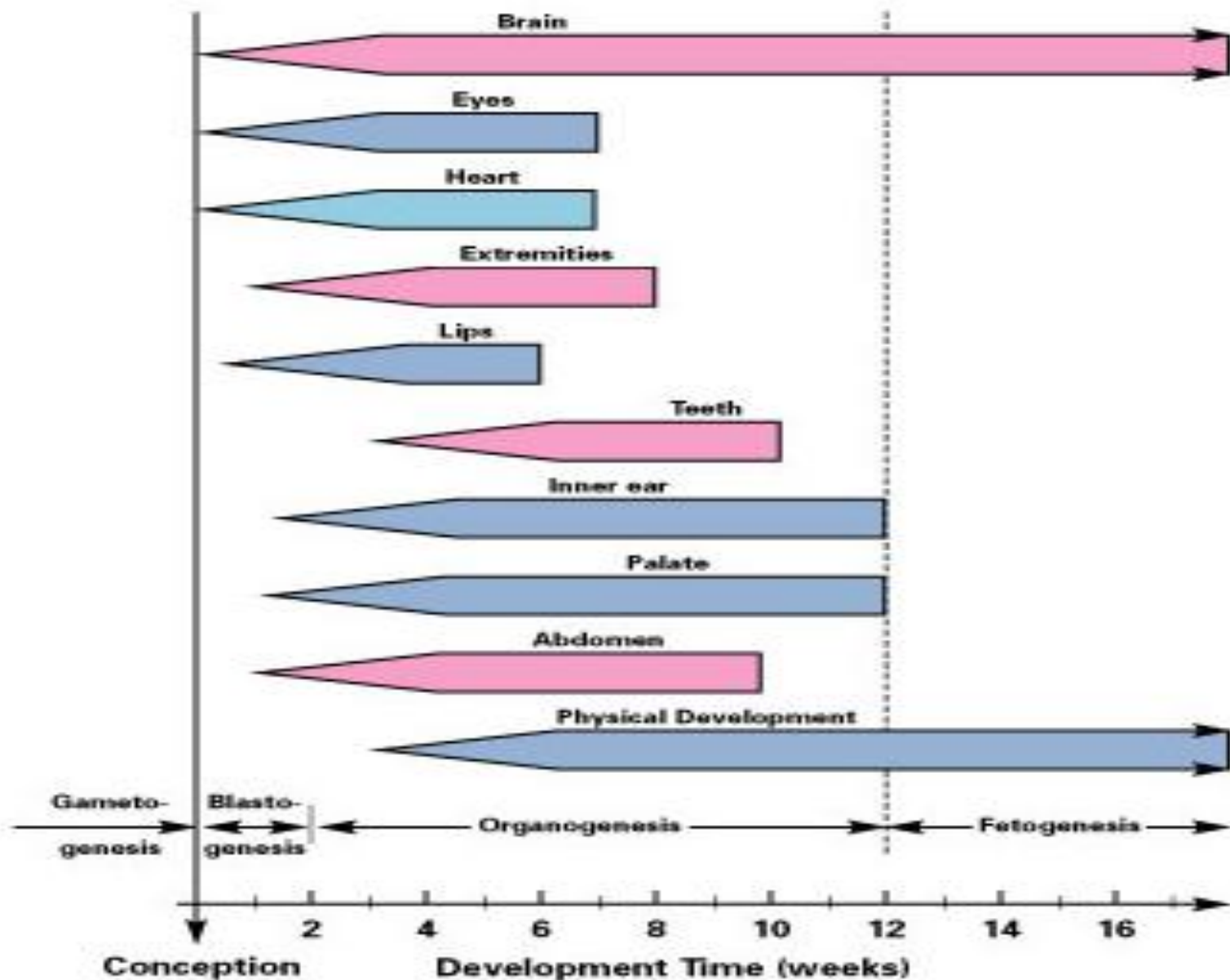
Distribution of congenital anomalies at birth,
ca. 2-5% of all newborns affected

Nervous system disorders are a leading cause of mortality in infants with congenital anomalies



- Nervous system
- Circulatory
- Digestive system
- Musculoskeletal system
- Other
- Heart
- Respiratory
- Genitourinary system
- Chromosomal

The concept of the “sensitive periods” of organogenesis





Teratology,

example of the thalidomide
catastrophe

Holzgreve, W., Carey, J., Hall, B., Lancet ii, 914-5, 1976

FETAL OUTCOME OF WARFARIN EXPOSURE

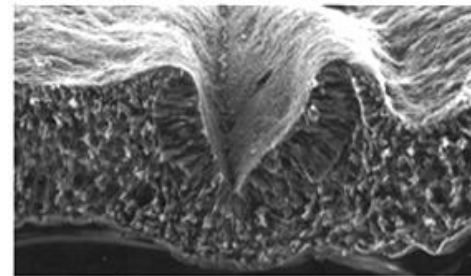
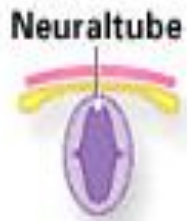
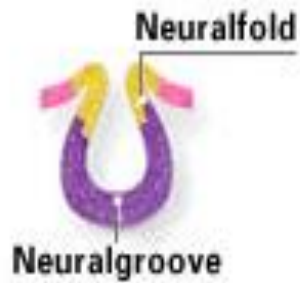
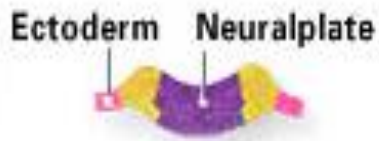
Outcome	Cases	%
<i>Abnormal liveborn (no haemorrhage):</i>	16	13.9
Exposure entire pregnancy	10	
Exposure after-12th week	5	
Exposure only 1st trimester	1	
<i>Fetal wastage</i>	15	13.0
<i>Neonatal haemorrhage</i>	1	0.9
<i>Other (very low birth-weight, neonatal death)</i>	1	0.9
<i>Normal child</i>	82	71.3
<i>Total</i>	115	100

What are Neural Tube Defects (NTDs)?

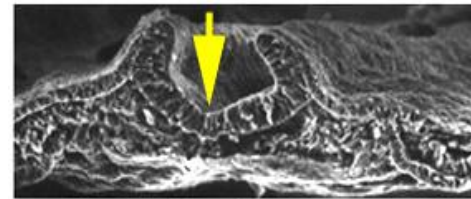
- Occur when the neural tube in newborns fails to close completely:
 - Failure of the neural tube to close over the lower spine causes spina bifida within the first 3 wks. of pregnancy
 - Failure to close in the region of the developing brain causes anencephaly or encephalocele



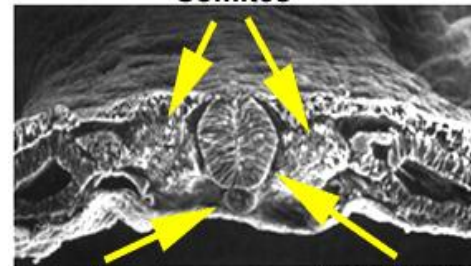
Development of the neural tube



Neural groove



Somites



Notochord

Neural tube

00-dB
hiedr
Tiefe

10/02/00

Bild #38 6.7 cm

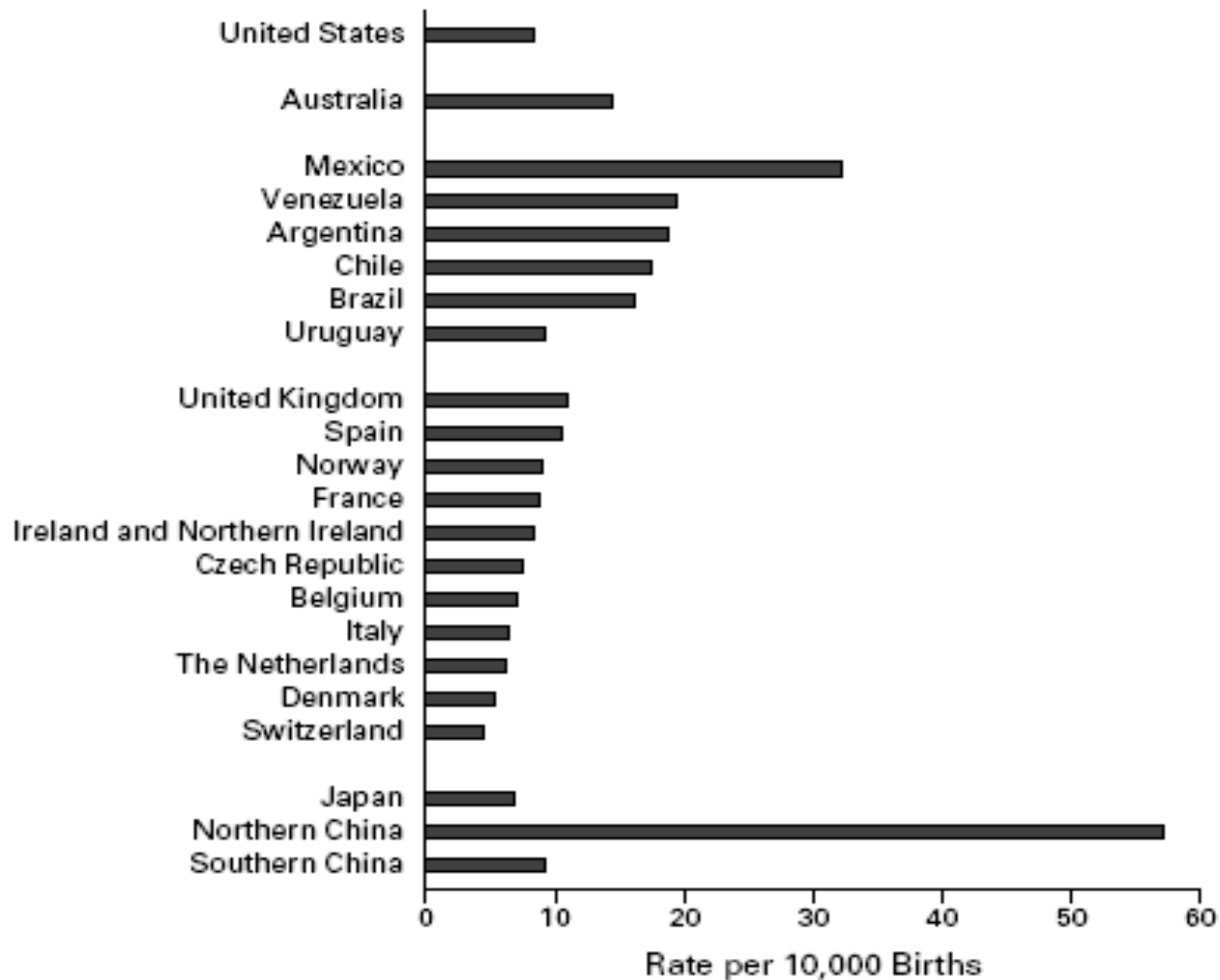








Rates of NTDs vary among regions





Causes of NTDs

- **Environmental and genetic factors have a joint role in causation**
 - Marked geographic and temporal variability
 - Ethnic background
 - Socioeconomic status
 - Nutrition

Folates – Forms of Vitamin B



Tomato



Broccoli



Orange

- Dietary folates - forms of the water-soluble Vitamin B
- Supplements

→ **Folic acid**

- synthetic, stable form of folate
- form commonly used for food fortification and vitamin supplementation

→ **Metafolin®**

- naturally occurring form of folate
- predominant form of folate in foods



Tomato



Broccoli



Orange

Tab. 3.4.1 Folatvorkommen in verschiedenen Lebensmitteln bzw. deren Nährstoffdichte (> Glossar) nach Bundeslebensmittelschlüssel (BLS) 1999

Lebensmittel	Folat-äquivalente µg/100 g	Nährstoffdichte µg /1000 kcal
Ei		
Hühnerei	27	159
Fleisch		
Rinderleber	242	1787
Huhn	5	25
Schwein	3	17
Rind	3	12
Fisch		
Thunfisch	7	24
Lachs	5	24
Hering	3	15
Makrele	1	6
Milch/Milchprodukte		
Weichkäse	42	108
Gouda	19	55
Magerquark	16	204
Vollmilch	4	65
Obst/Früchte		
Apfelsinen	31	643
Avocado	30	141

Tab. 3.4.1 Folatvorkommen in verschiedenen Lebensmitteln bzw. deren Nährstoffdichte (> Glossar) nach Bundeslebensmittelschlüssel (BLS) 1999 (Forts.)

Lebensmittel	Folat- äquivalente µg/100 g	Nährstoff- dichte µg /1000 kcal
Orangensaft	16	442
Bananen	16	178
Erdbeere	15	467
Äpfel	4	74
Cerealien		
Roggen- vollkornmehl	38	126
Weizen- vollkornmehl	31	94
Reis (ungeschält)	13	36
Reis (geschält)	6	49
Gemüse		
Spinat	56	3141
Weißkohl	36	1482
Broccoli	25	956
Salat	23	1702
Rosenkohl	23	600
Tomaten	20	1061
Bohnen (grün)	15	494
Spargel	13	716
Blumenkohl	8	380



The risk of a neural tube defect decreases as maternal folate status increases

RBC folate level, nmol/L	Percent of women ¹	Risk increase ²
<340	3%	8-fold
340–453	14%	4-fold
453–680	48%	3-fold
680–906	22%	2-fold
>906	13%	–

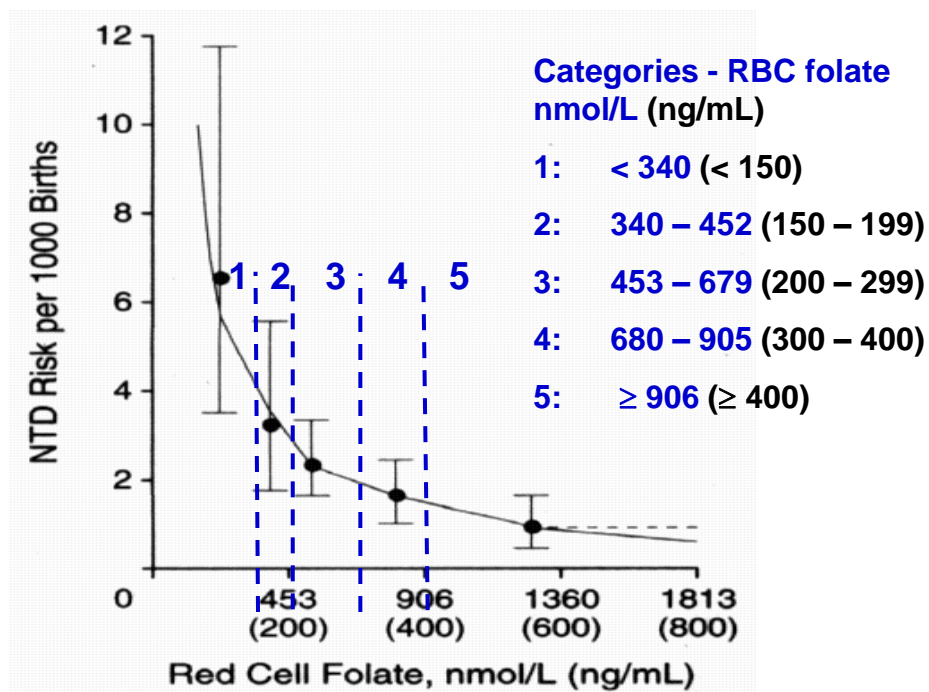
Folate Intake Options

- Natural Foods
- Supplementation
- Fortified Foods



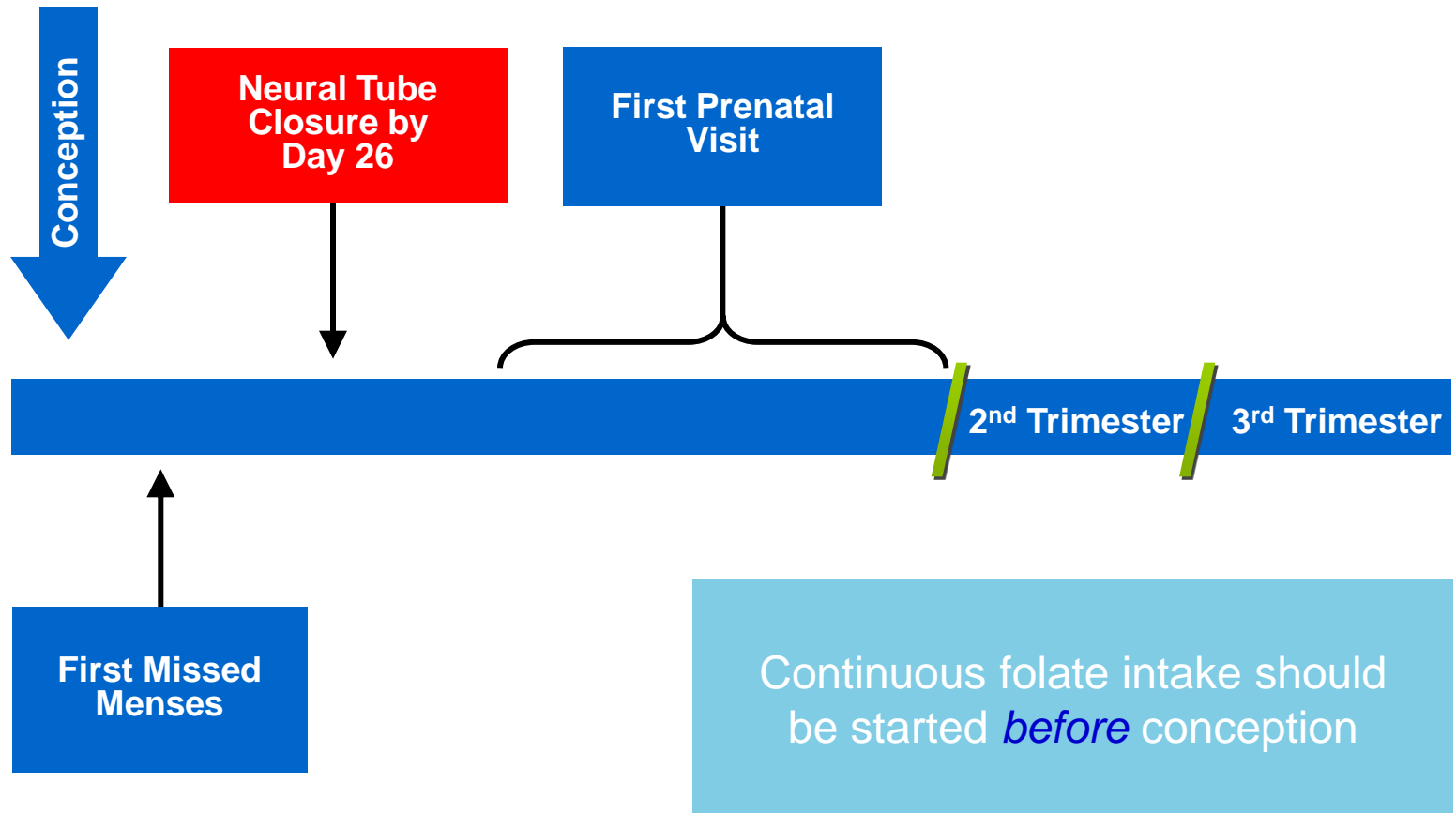
Folate Levels as a NTD risk factor

- The occurrence of NTD is directly linked to insufficient folate levels during preconception and early pregnancy.
- NTD risk declines markedly with improved folate status



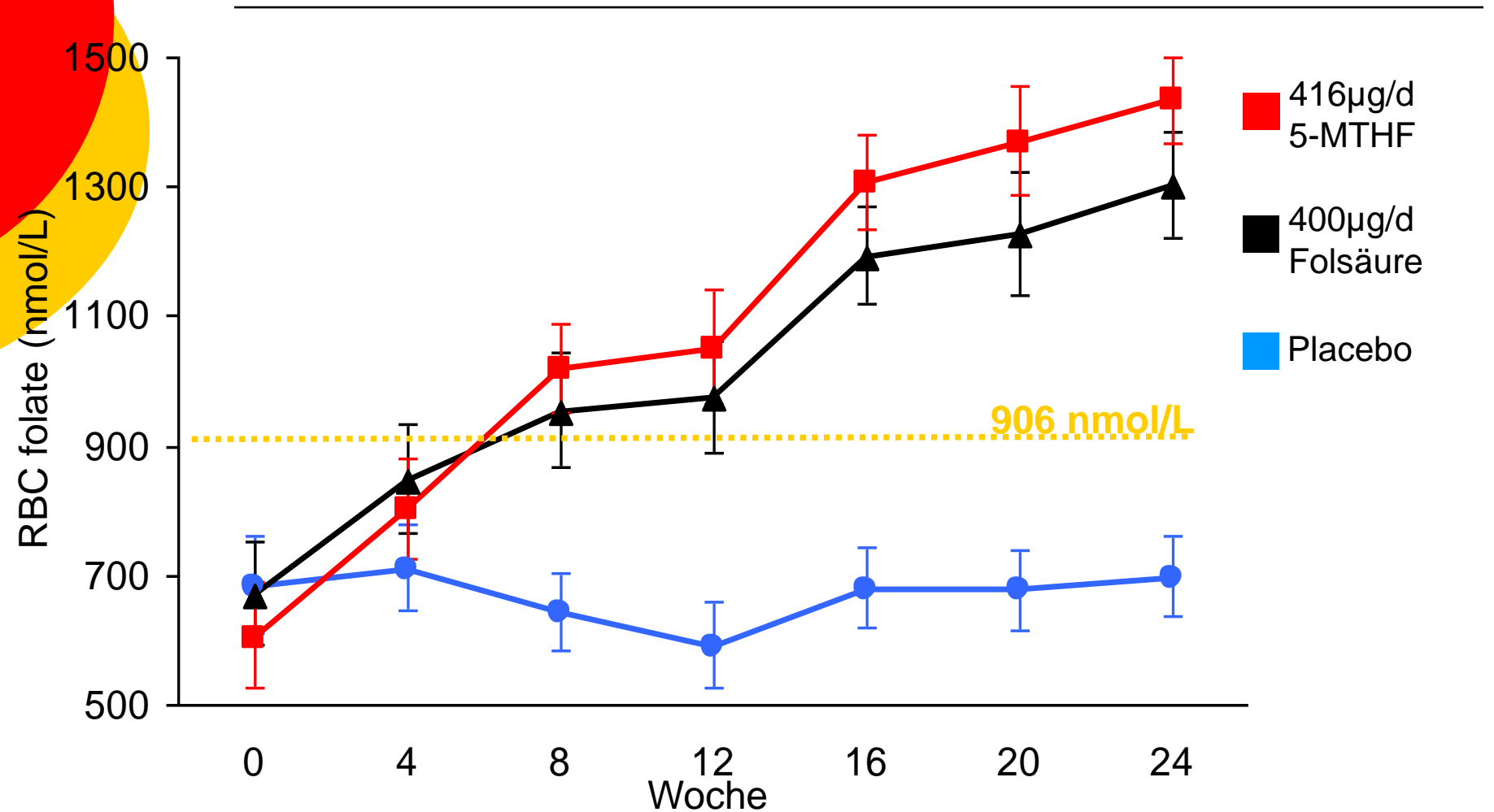
Timing of folate intake is important!

Neural tube closes before pregnancy diagnosis



Erythrocyte foate levels (nmol/L)

(Data presented as geometric means (95% CI))





Benefits of Folic Acid Supplementation on Pregnancy

Folate supplementation reduces the risk of neural tube defects

		Neural tube defects	
	Offspring	Expected number	Observed number
Vitamin supplement containing folic acid 800 µg	2,471	6.9	0
Trace element supplement	2,391	6.7	6

Summary of Results of the Hungarian Clinical Trial

Major Malformations	Elevit Pronatal	Placebo Group
Neural-tube defect (SB)	0	6
Urinary tract defect	2	9
Cardiovascular malformation	10	20
Limb deficiencies	1	5
Hypertrophic pyloric stenosis	2	8
Orofacial clefts	4	5
Other	32	44
Total	51	97



Recommendations for periconceptional folate supplementation



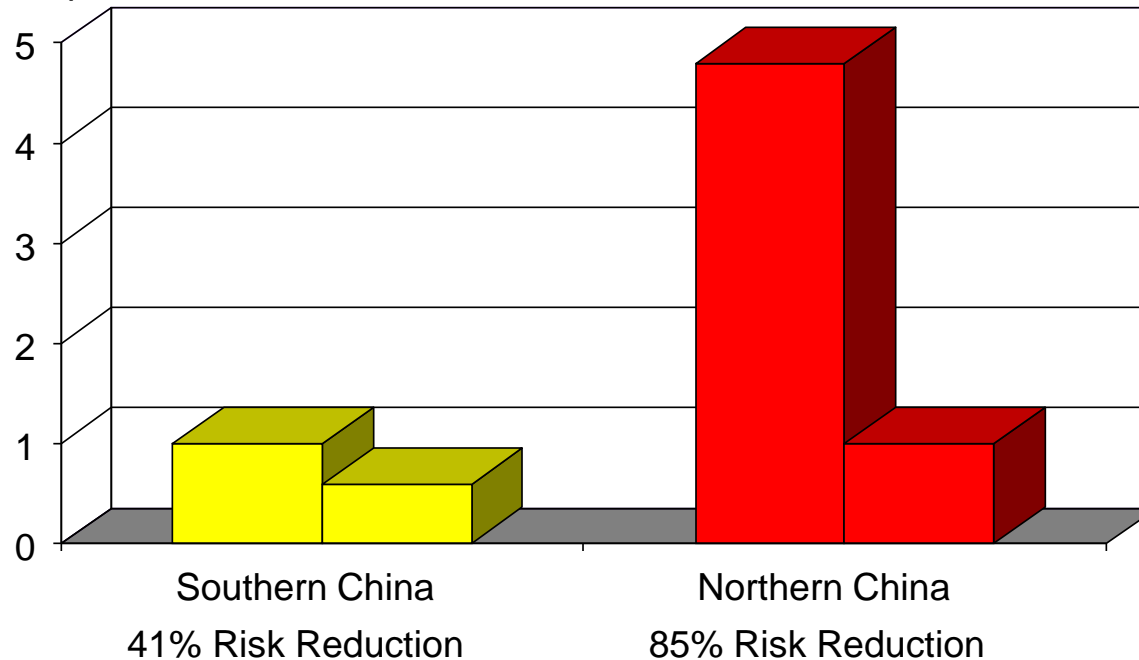
Folate supplementation recommendations: USA

- The Centers for Disease Control and the US Preventive Services Task Force recommends that
 - All women of childbearing age in the United States who are capable of becoming pregnant should consume at least 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs”
- This recommendation should be followed before conception and during early pregnancy

Significant NTD risk reduction in China

- Evidence of the **0.4 mg** folic acid dosing recommendation
- Analysis of 247,831 Pregnancy Outcomes

NTDs per 1000 births





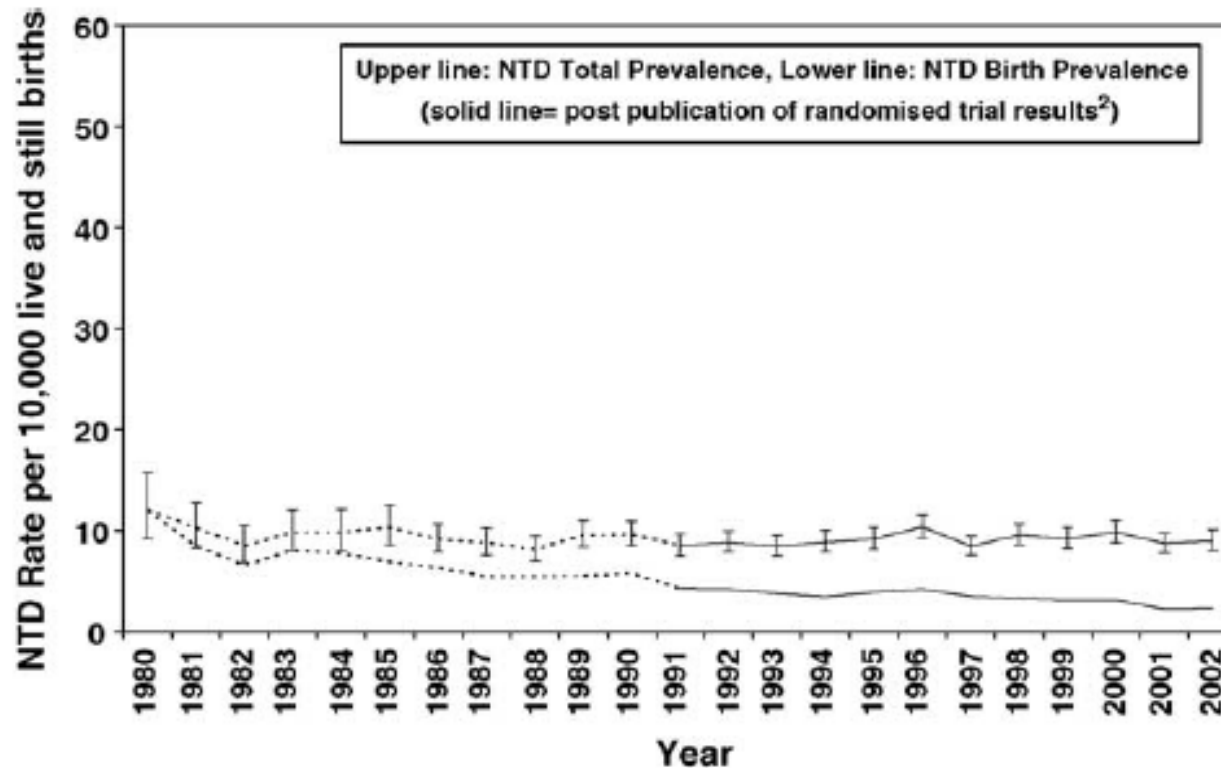
Folate supplementation recommendations vary throughout Europe

- Periconceptional folate supplementation recommendations vary across Europe¹
 - 13 countries have government policies regarding folate supplementation
 - 7 countries have implemented government-led health education initiatives
 - The recommended daily dose of folic acid varies by country (0.4 mg of folic acid in the majority of countries)
 - The recommended window of intake varies by country



Maria Walliser mit Familie: Der Ex-Skistar wirbt seit Jahren für Folsäure. Tochter Siri kam behindert zur Welt.

The potential for preventing neural tube defects remains unfulfilled in Europe

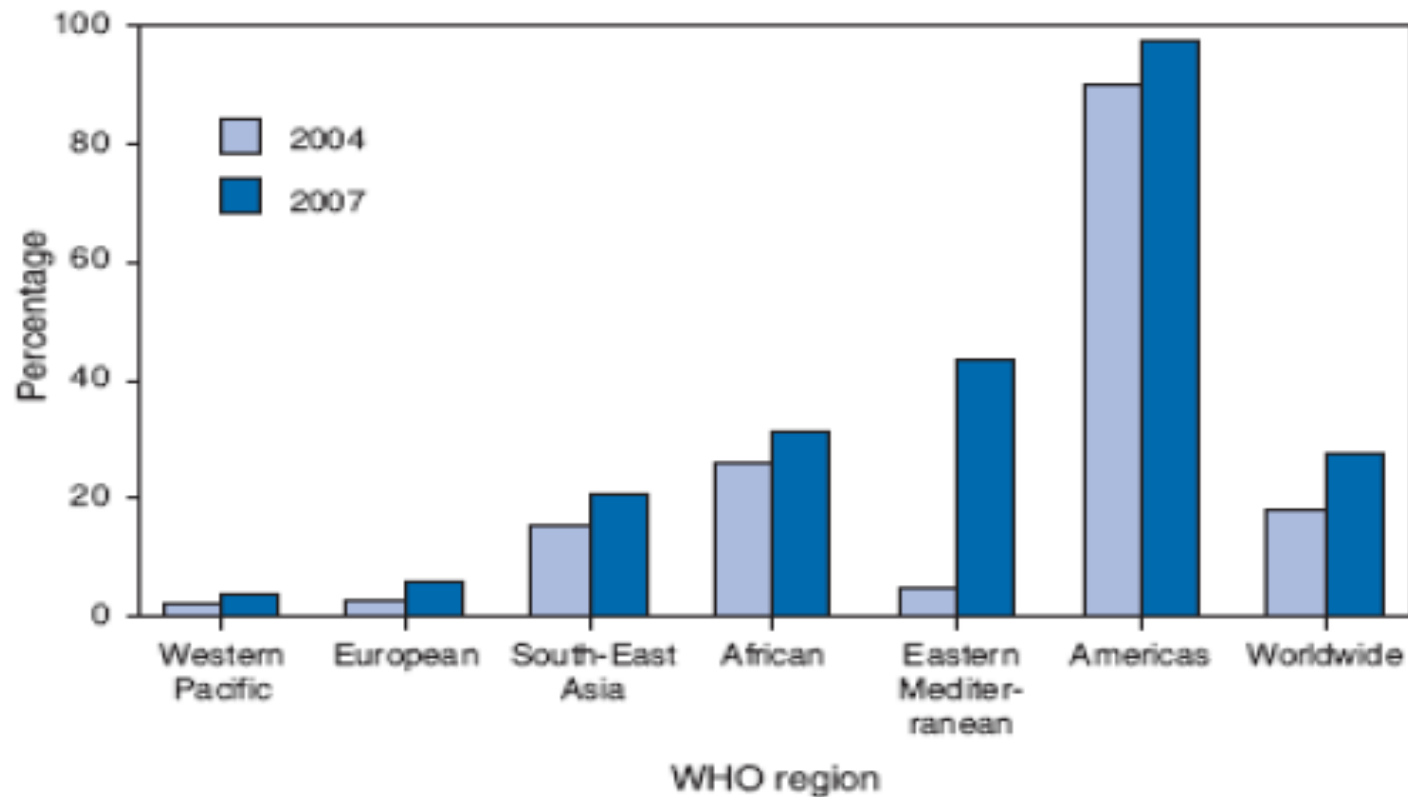


¹Busby et al. *Reprod Toxicol* 2005;20:393–402



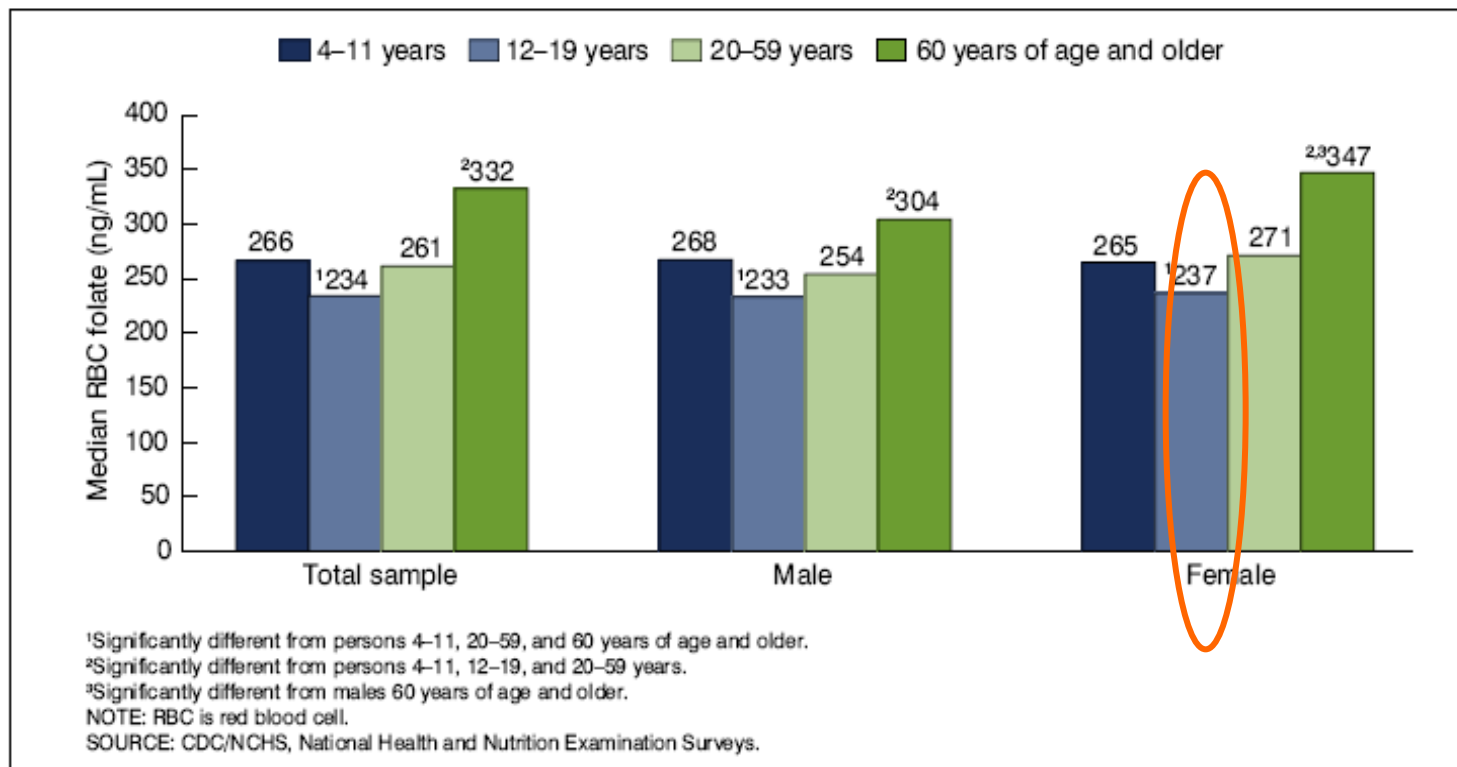
Food fortification

The uptake of food fortification programs varies according to geographic region

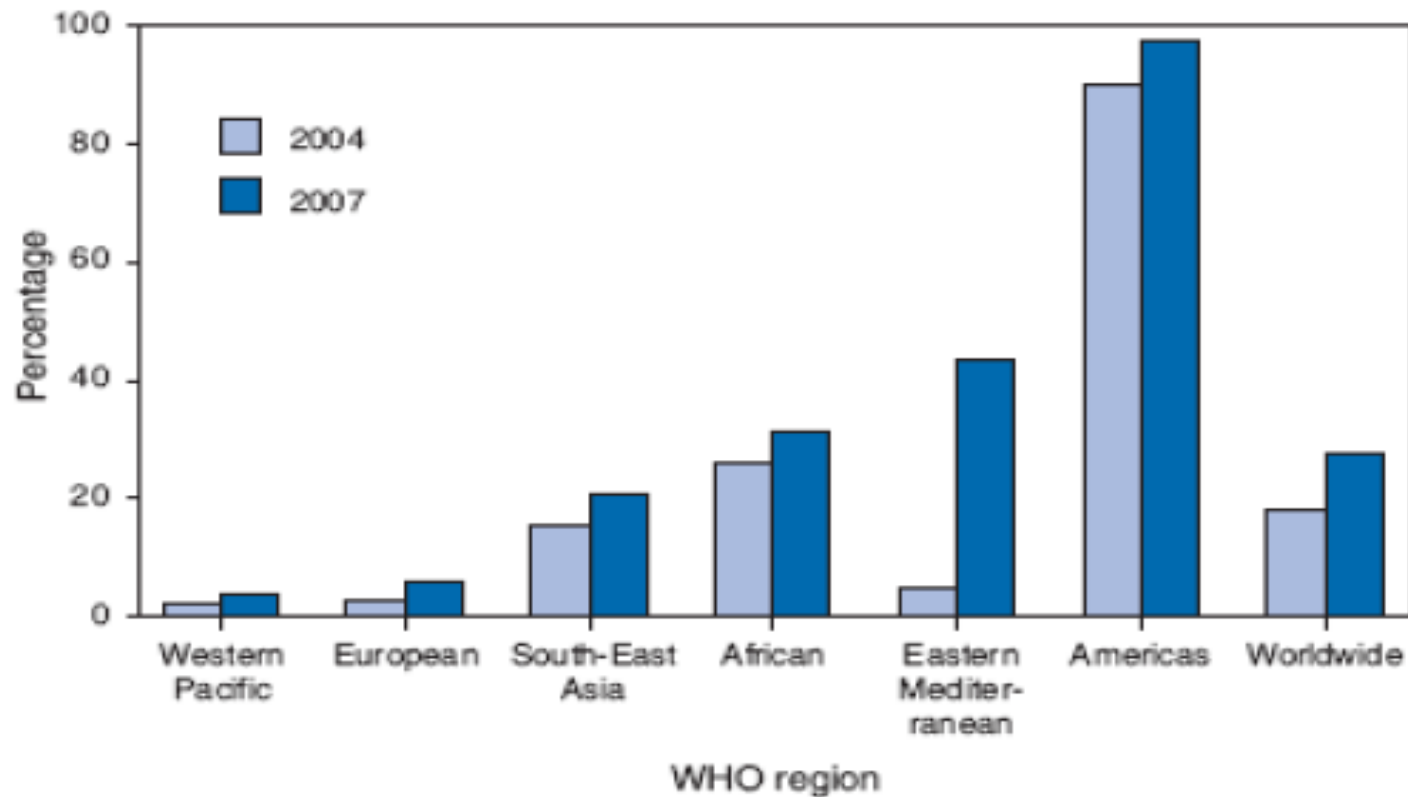


Adolescent women in the USA have low levels of folate despite food fortification

Figure 3. Median RBC folate levels by sex and age: United States, 2005–2006



The uptake of food fortification programs varies according to geographic region





Shall we put the world on folate

„A high risk intervention strategy could be considered targeting women at reproductive age ... rather than putting entire nations on folate“

Osterhues, A., Holzgreve, W., Michels, K.B.

University of Freiburg, Germany (AO, WH, KBM), and Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA)

Lancet 2009



Oral Contraceptives plus Folates - The Rationale



Users of oral contraceptives are women of childbearing age

- Users of oral contraceptives (OCs) represent those members of the population in whom adequate levels of folate are of the greatest benefit
- Fortifying an OC with a folate is a targeted approach to folate supplementation
 - Food fortification reaches all members of society, including men, children and the elderly



Physicians will gain a unique counseling opportunity

- Women who use OCs are seen and examined regularly by their physician
- Physicians will gain a unique opportunity to counsel women about the benefits of folate supplementation when their focus switches from contraception to conception
 - Approximately one-half of women who intend to become pregnant stop using contraception without consulting a physician¹
 - Physicians are only aware of their patients' plans to become pregnant approximately 50% of the time¹

¹Data on file, Bayer Schering Pharma AG




A significant number of pregnancies are unplanned

- Approximately 1,000,000 women per year in the USA become pregnant while taking contraceptives¹
- Women using OCs are less likely to consume sufficient levels of folate
 - Their focus is on the prevention of pregnancy and not the prevention of possible birth defects
- Unplanned pregnancy is one of the prevalent maternal features associated with low preconceptional folic acid use^{2,3}



Women became pregnant very quickly after stopping oral contraceptives

- Rapid conception is possible after OC cessation
 - 21.1% of women become pregnant after 1 cycle
 - 45.7% of women become pregnant after 3 cycles
 - 79.4% of women become pregnant after 13 cycles
- NTDs occur during the 28-day period following conception, often before a woman realizes she is pregnant



An oral contraceptive could be an ideal vehicle for folate supplementation in women of childbearing age

- Women would receive folate on a regular basis
 - Many women find it difficult to remember to take a multivitamin on a regular basis
 - Only 33% of fertile-aged women take folic acid supplements on a daily basis¹
 - Compliance to OCs is generally high”
- **OC PLUS SHOULD HOPEFULLY AVAILABLE SOON**



The „Plus“ concept follows the old
English motto

**An ounce of prevention is better
than a pound of cure**

(A microgram of prevention is
better than a kilogram of cure)

Thank you for your kind
attention

