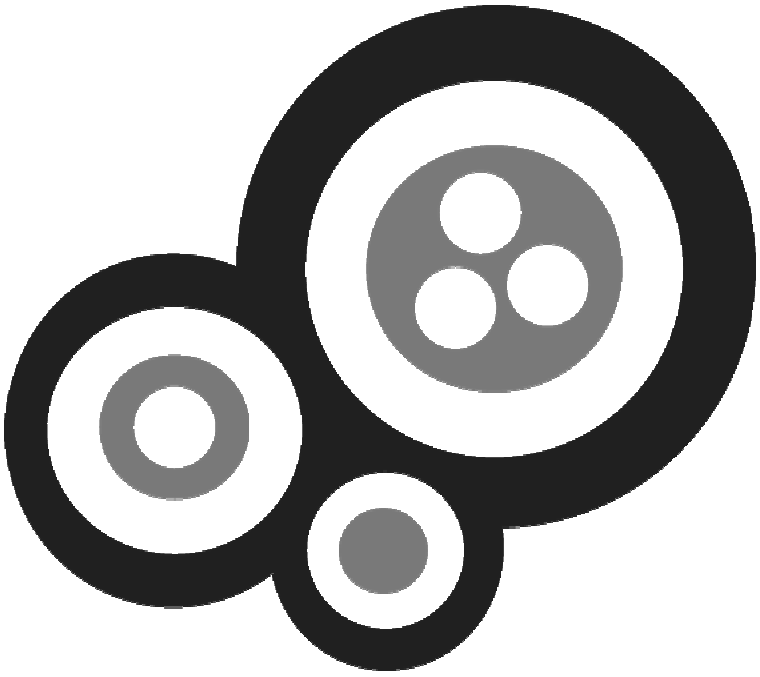

PLENARY 4

FOLIC ACID AND PREVENTION OF BIRTH DEFECTS

Moderators:
Andrew Czeizel – Hungary
Joseph Mulinare – USA

FOLIC ACID AND PREVENTION OF PRETERM BIRTH – A POPULATION-BASED STUDY

[1]Andrew E. Czeizel, [2]Erzsebet Horvath-Puho, [3]Nandor Acs, [3]Ferenc Banhidy

[1] Foundation for the Community Control of Hereditary Diseases, Budapest, Hungary
[2]Hungarian Congenital Abnormality Registry, Budapest, Hungary
[3] Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

Background: The rate of preterm birth is high in Hungary and recently there have been reports of decreased rate of preterm births and increased weight of newborns of pregnant women who have taken folic acid and/or multivitamins during their pregnancies and we decided to check these findings in our population..

Methods: The population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities including 37,777 newborns without birth defects was evaluated. Medically recorded gestational age at delivery and birth weight, rate of preterm birth and low birthweight were compared in newborns of 19,334, 694, 1,441 mothers with folic acid alone, multivitamin, multivitamin + folic acid supplementation during pregnancy, respectively, and 16,308 newborns of pregnant women without folic acid/multivitamin supplementations as reference.

Findings: Mean birth weight exceeded by 30, 75 and 70 gram the values of reference sample (3,257 g) after folic acid alone, multivitamin, multivitamin + folic acid supplementation during pregnancy. Mean gestational age was 0.3, 0.2, 0.5 week longer in the groups of folic acid alone, multivitamins and multivitamin + folic acid than the reference mean gestational age (39.2 wk). The rate of low birthweight newborns did not decrease significantly, while the rate of preterm births was lower in all supplementation groups, particularly after multivitamin + folic acid (5.1%) compared with the rate of preterm births in the reference sample (11.2%). High dose of folic acid alone in the third trimester resulted in 0.5 week longer gestational age, with a significant reduction in the rate of preterm births (5.4%).

Interpretation: The significant reduction in the rate of preterm births (30-57%) after folic acid or multivitamin supplementation during pregnancy is of clinical importance.

PREVENTION OF SPINA BIFIDA AND ANENCEPHALUS (SBA): ASSESSING THE WORLDWIDE APPROACHES TO AND THE IMPORTANCE OF FOLIC ACID FORTIFICATION OF FLOUR

Joseph Mulinare

Prevention Research & Health Communication Team, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, USA

Many countries around the world are currently fortifying wheat flour with micronutrients including iron, folic acid, and other B vitamins. Fortification of flour with folic acid has been shown to be an effective, sustainable and cost-effective intervention to eliminate folate insufficiency and reduce the occurrence of spina bifida and anencephalus (SBA). There is solid evidence from developed countries like United States, Canada, Costa Rica, and Chile that shows regular consumption of foods containing folic-acid fortified flour leads to substantial increases in serum and red blood cell folate levels. Data from birth defects monitoring systems from before and after the implementation of these flour fortification programs have also shown notable reductions in the occurrence of babies affected with SBA. Folate insufficiencies represent an important and evolving global health challenge that contributes to the global burden of serious birth defects. This presentation will review what we know about folic acid fortification and why it is so important for the prevention of birth defects.

IMPACT OF FOLIC ACID FOOD FORTIFICATION IN SOUTH AMERICA

[1]Eduardo E. Castilla, [2]Ieda M Orioli, [3]Jorge S Lopez-Camelo

[1]ECLAMC at Oswaldo Cruz, Institute, Rio de Janeiro, Brazil
[2]ECLAMC at Rio de Janeiro Federal University, Brazil
[3]ECLAMC at IMBICE-Conicet, La Plata, Argentina

Three South American countries adding up to almost four million births per year, have folic acid food fortification policies aim o the prevention of neural tube defects (NTD), and other congenital anomalies. Their annual numbers of live-births are 3,078,204 in Brazil, 663,685 in Argentina, and 243,848 in Chile. Chile started fortifying wheat four with 2.2 g/Kg in January 2000, Argentina also wheat flour with the same dosage in Nov ember 2003, and Brazil wheat and corn flours with 1.5 g/Kg in June 2004. ECLAMC, having permanently surveyed birth defects in these countries for the past 40 years, is in a good position to monitor the impact of fortification. In the case of Chile the analytical situation is easier than in the other two countries because the pre-fortification baseline for NTDs is higher, and the secular trend stable, while the latter was significantly decreasing since the early 1990s. Baseline values were derived from births occurred two years previous to the start of fortification, while the fortified period was counted starting one year after that date. In Chile, only NTD showed a significant decrease, without differences registered for oral clefts, Down syndrome, cardiac or renal anomalies. Spina bifida decrease attained close to 50% (47%) after 13 months of fortified births sample. The decrease was less marked for anencephaly, for lower (lumbar-sacral) than higher (cervical, thoracic), and for isolated than associated spina bifidas. In Argentina, similar observations than in Brazil were made. However, due to the pre-fortification decreasing trends for NTDs, larger samples sizes than those available are needed. In Brazil, no significant de crease was proven for NTDs, or any other congenital anomaly type.

BENEFICIAL CARDIOVASCULAR EFFECTS OF FOLIC ACID: FROM PREVENTING CONGENITAL HEART DEFECTS TO REVERSING HEART FAILURE

An L. Moens

Div. of Cardiology, Laboratory of Molecular Cardiology,
University of Antwerp, Antwerp, Belgium &
Johns Hopkins Medical Institutions, Baltimore, USA

The aetiology of nonsyndromic congenital heart defects is complex, involving both genetic, epigenetic, and environmental risk factors. However, one of the most promising clues about prevention of conotruncal defects (truncus arteriosus, transposition of great arteries and tetralogy of Fallot) is that women who use vitamins containing folic acid in early pregnancy have reduced risks of delivering offspring with conotruncal defects. Folic acid is well-known for its preventive effect on neural tube closure, which depend on NO synthase (NOS) activity. Indeed, blocking NOS activity by inhibiting its cofactor BH4 or its calcium-calmoduline binding to NOS, results in ablated closure of the neural tube. Folic acid, well-known for its homocysteine-lowering effect, can interact with endothelial nitric oxide (eNOS) by increasing the bioavailability of tetrahydrobiopterin (BH4), an essential cofactor of eNOS.

In this study we investigated the mechanism of action of folic acid using rodent-models of myocardial remodeling. We found that the beneficial cardiovascular effects of folic acid can be explained by preventing NOS-uncoupling, by its pronounced direct antioxidant effects (superoxide scavenging) and by the prevention of the myocardial energy-metabolism. The latter can be explained because folic acid upregulates IMP-biosynthesis. As a consequence of this, folic acid preserves the ATP/ADP-pool in the myocardium.

Therefore, we can conclude that folic acid has a beneficial role via its direct interaction with NOS. This mechanism explains both the preventive effect on congenital and remodeling disorders.

VIEW FROM THE DISABILITY WORLD ON THE IMPORTANCE OF PRE-CONCEPTION FOLIC ACID

Pierre Mertens

International Federation for Spina Bifida and Hydrocephalus, Brussels, Belgium

Persons with Spina Bifida make this need for prevention visible, but from our perspective you can ask the question: why should we prevent who we love? As a parent of a daughter with Spina Bifida, Liesje, I was confronted with this question and I will try to answer it elaborating 3 main points:

(1) Prevention always relates to the future, to tomorrow. Prevention measures for the next generation should not have a judgement about the value of the life of any person with Spina Bifida and/or Hydrocephalus now. The associations for Spina Bifida in many countries themselves took the lead for prevention defending the value of their lives questioning secondary prevention.
(2) It is an established fact that a daily intake of 0.4 mg of folic acid, at least one month prior to conception and during the first three months of pregnancy, considerably reduces the incidence of Spina Bifida and Hydrocephalus. But informing and influencing the general population is very difficult. Therefore IF is also advocating for mandatory fortification of staple foods, like flour, with Folic Acid. The Flour Fortification Initiative was and is a great partner in influencing governments' decision making in this matter.
(3) Next to prevention, there is a need for research on the causes of the deficit of folate in the mother's blood. By systematically eliminating unborn children with the impairments, the symptoms disappear and we risk the cause remains unknown. As a result, together with Spina Bifida in the North, research grants for further investigation are being eliminated.

Coming back to my question; should we prevent who we love?

No, we have to take care for whom we love. By taking care we see their valuable lives, but also their problems. If we can prevent these problems to newborns, we should do it.

When Lies died I did not miss her wheelchair.
I missed Lies,
her smile,
her heart,
her love.

It is because we love, we prevent.