Session I. Plenary lecture

PRIMARY PREVENTION: THE MODEL OF FOLIC ACID

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Introduction

Birth defects are an important public health problem with an incidence of around 3%. A group of birth defects are Neuronal Tube Defects (NTDs) which are one of the major causes of perinatal mortality.

NTDs include certain central nervous system malformations such as anencephaly, encephalocoele and spina bifida, which occurre during embryonic development and neural tube closure between the 17th and 30th day after the conception.

The location of the defect along the neuraxis determines the specific anomaly presented: if the cephalic end of the tube is affected, the outcome is the lethal condition anencephalus, or more rarely encephalocele or iniencephalus; if any of the remainder is affected, the outcome is spina bifida. Many neonates with spina bifida and encephalocele survive but the vast majority has lifelong moderate or severe disability including lower limb paralysis, poor bladder control, and intellectual impairment.

Approximately 4,500 pregnancies every year in Europe result in a LiveBirth (LB), StillBirth (SB) or Termination of Pregnancy (TP) of a baby/foetus affected by a NTDs, mainly anencephaly and spina bifida.

In Italy, the anencephaly prevalence was 2.23/10,000 LB, SB, TP from 1996 to 2002, while the prevalence of spina bifida was 3.28/10,000 and 0.80/10,000 for encephalocele. These data have been elaborated in the frame of a collaboration among the National Centre for Rare Diseases of the Istituto Superiore di Sanità and Italian Registers of Congenital Malformations, namely: Campania Register of Congenital Malformations (Registro Campano dei Difetti Congeniti, RCDC), Emilia-Romagna Register on Congenital Malformations (*Indagine sulle Malformaizoni congenite in Emilia Romagna*, IMER), North-East Italy Register of Congenital Malformations (*Registro Nord-Est Italia delle malformazioni Congenite*, Registro NEI), Sicilian Register of Congenital Malformations (*Indagine Siciliana Malformazioni Congenite*, ISMAC) and Tuscany Register of Congenital Malformations (*Registro Toscano dei Difetti Congeniti*, RTDC) (1).

NTDs have a multifactorial aetiology, i.e., they arise from the interplay between genetic predisposition and environmental risk factors. The genetic basis is indicated by a number evidences such as the significantly increased risk of recurrence in families that already had an affected child. Among environmental factors, the inadequate intake of Folic Acid (FA), appears to play a major role; as a consequence, increasing the intake of FA, in the periconceptional period can represent a powerful tool for primary prevention of NTDs.

Folic acid

FA (or B9 vitamin) is a vitamin belonging to the B group. It is essential for metabolism of sulphur-amino acids and nucleic acids: accordingly, biological processes with high cell proliferation rate are specifically vulnerable to FA deficiency, such as haempoiesis and embryogenesis. FA is present as folate in several green-leaf vegetables and other food commodities such as spinach, chard, asparagus, artichokes, bruxelles sprouts, citrus, oranges, strawberries, beans and nuts.

Evidence of a possible association between folic acid and NTDs has been described in the scientific literature for more than three decades.

Increased folic acid intake is associated with significantly fewer NTDs in combination with another major birth defect, particularly orofacial clefts, cardiac and limb defects and omphaloce (2).

Folic acid deficiency has been suspected as contributing to NTDs as far back as the 1970s, but the conclusive proof was not demonstrated by large intervention studies until the mid-1980s and early 1990s. In 1976, Smithells *et al.* (3) published an early paper suggesting that deficiencies in FA and/or other micronutrients may predispose developing foetuses to NTDs. In a subsequent paper in 1980, Smithells *et al.* (4) reported on possible prevention of NTDs by periconceptional vitamin supplementation.

In the 1990s, multiple intervention trials demonstrated a substantial reduction in the incidence of NTDs with preconception folic acid treatment (2).

These studies include a British Medical Research Council (MRC) study in which women with a previous history of a pregnancy affected by an NTD were treated with large doses of FA (3). This trial has been estimated that improving folate status sufficiently would result in the prevention of 72% of all NTDs.

In a systematic review effected by Lumley *et al.* (6) has been estimated that periconceptional folate supplementation reduces the prevalence of neural tube defects substantially: relative risk (RR) 0.28 (95% confidence interval (CI) 0.13, 0.58). The reduction is both for occurrent defects (those where the mother has not had a previously affected foetus or infant) RR 0.07 (95% CI 0.00, 1.32) and for recurrent defects (where the mother has had a previously affected infant) RR 0.31 (95% CI 0.14, 0.66).

The trials had very low power to identify differences in limb reduction defects RR 0.59 (95% CI 0.04, 8.34), conotruncal defects RR 0.74 (95% CI 0.16, 3.32), or orofacial clefts RR 0.76 (95% CI 0.24, 2.37) or all other major birth defects combined RR 0.76 (95% CI 0.38, 1.51) (6).

Normal daily requirement for FA is 0.2 mg but it doubles during pregnancy, due to the higher requirement for embryonic development. FA is currently used in several Countries for primary prevention of NTDs; much evidence exists that a significant reduction in the incidence can be achieved, especially in the high-incidence areas. In Italy, this public health practice has still an insufficient development.

Three approaches could be adopted to increase folic acid consumption among women in fertile age:

- The first is increase dietary intake of folate rich foods such as green leafy vegetables and fresh fruit.
- The second involves population health promotion programs to encourage women to take FA supplements periconceptionally, whose effectiveness is supported by a large number of studies. It is noteworthy that effectiveness could be further increased by the proper identification of factors (e.g., drugs, metabolic conditions, lifestyles) that may enhance FA requirements and/or impair FA metabolism.
- The third is the fortification of foods with FA. The food fortification (especially of wheat flour) adopted as a mandatory policy in several non-EU countries (USA, Canada, Chile

and Costa Rica) to provide a supply of FA to all women in fertile age, independently from pregnancy planning. Compared to supplementation, fortification gives a lower risk reduction whilst covering a wider basis of population.

Promotion of folic acid intake in Italy

In Italy, a network for the promotion of FA for the prevention of congenital defects has been formed and coordinated by the National Centre for Rare Diseases (Istituto Superiore di Sanità, Rome, Italy) together with other institutions. The Italian network for FA promotion was established in April 2004, in order to integrate and optimize the many different activities in course at local or regional level. Different organisations including research institutes, university departments, scientific societies, registers, regional offices and councils, patient associations and newspapers met together to propose and agree recommendations regarding folic acid supplementation. 190 national and 2 international organisations are now part of the network (Figure 1).

Figure 1. Distribution of the Italian Network organizations by Region

The Network operates thought the following working groups: “Advocacy”, “Pharmaceuticals and diet integrators”, “Education of health care workers”, “Information of the general population”, “Research”, “Surveillance and evaluation”.

Some activities undertaken by the Italian network for the promotion of FA are as follow:
- development of communication strategy for FA promotion;
- development of information, education and communication materials;
- organisation of an awareness week on prevention on neural defects;
- risk and benefit analysis of the folic acid;
- evaluation of the prevalence of congenital malformation preventable by the intake of folic acid;
- development of an education model for the promotion of acid folic in schools.

The recommendation regarding FA supplementation was approved in November 2004 and is as follows:

> it is recommended that all fertile women that plan a pregnancy or do not actively exclude the possibility take at least 0.4mg a day of FA. It is fundamental that FA is taken starting at least a month before conception and for the whole first trimester of pregnancy. Women who have had prior NTD-affected pregnancy are at higher risk of having a subsequent affected pregnancy as well as women affected by diseases such as diabetes, etc should assume 4-5 mg of FA every day.

The recommendation, together with more details (why, how much, when, foot notes explaining the choice) and a list of scientific publications that support the recommendation is now freely accessible at http://www.iss.it/cnmr/.

References

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