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Primary prevention of congenital anomalies and the role of folic acid

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Review article

Abstract
Congenital anomalies are an important diagnostic group in the perinatal healthcare. Only some of these anomalies have an individual cause (complex anomalies accompanying chromosomal aberrations, congenital anomalies with monogenic inheritance, typical anomalies caused by strong teratogens etc.). The majority of cases of congenital anomalies is caused by multiple and complex factors that are hard to identify. Therefore – the so called primary prevention of congenital anomalies becomes much more important during last years. Primary prevention of congenital anomalies itself is composed of various guidelines and recommendations that should prevent the formation of the anomaly. Specific role in the primary prevention has the folic acid supplementation that is world-wide recommended as the prevention of neural tube defects.

Key words: congenital anomalies, prevention, folic acid

PRIMÁRNÍ PREVENCE VROZENÝCH VAD A ÚLOHA KYSELINY LISTOVÉ

Přehledový článek

Abstrakt
Vrozené vady představují v oblasti perinatální péče velmi významnou skupinu diagnóz. Pouze u některých případů můžeme jejich příčiny jasně určit (komplexní vady u chromozomových aberací, vrozené vady s monogenním typem dědičnosti, typické vrozené vady způsobené dokumentovatelným působením teratogenů velkého účinku apod.). Ve většině případů vznikají vrozené vady na základě uplatnění více faktorů, které lze v daném konkrétním případě jen obtížně identifikovat. V poslední době je proto kladen zvláštní důraz na tzv. primární prevenci vrozených vad. Ta je tvořena komplexem postupů a doporučení, jejichž účelem je zabránit samotnému vzniku vrozené vady. Specifickou roli zde pak má plánované užívání kyseliny listové v perikoncepčním období, které je celosvětově doporučováno jako prevence vzniku poruch uzávěru neurální trubice.

Klíčová slova: vrozené vady, prevence, kyselina listová

Introduction

Congenital anomalies are deviations from the normal prenatal development. The widely used term "congenital developmental anomaly", or just "congenital anomaly" (CA) refers to a prenatally originated deviation diagnosed in a born child, but it is also used in a general sense. The diagnosis of congenital anomaly constitutes a medical, socio-economic and frequently also an ethical problem – a problem which is not rare. According to the data of the National Register of Congenital Anomalies of the Czech Republic (maintained with the Institute of Health Information and Statistics of the Czech Republic), approximately 3% – 5% of children are presently born with some type of congenital anomaly in the Czech Republic (1).

From a medical viewpoint, the term is extremely broad: CAs may affect practically any organ structure, and their clinical importance varies as well – ranging from minor cosmetic defects not significantly influencing the medical condition of the person affected, and ending with critical, life-threatening CAs – or those incompatible with life (2).

Basic measures in mother and child care to influence the frequency of CA in born children include prenatal screening and targeted prenatal diagnostics. In the Czech Republic – as in a number of other countries – applicable legislation allows terminating pregnancy if a severe CA of the fetus incompatible with normal postnatal development has been diagnosed (3). The exact conditions of the procedure, including applicable time limits, are stipulated by the relevant laws and decrees. The numbers of prenatally diagnosed CAs has been growing in the Czech Republic – for instance, more than 80% of Down Syndrome cases is now diagnosed prenatally (3).

For some years now, other procedures to prevent CA have been gaining ground within the care for pregnant women: these are referred to as "primary prevention of CA" methods. As the name implies, these preventative measures aim to prevent the CAs from occurring in the first place; therefore procedures and recommendations used within the primary prevention of CAs focus mainly on the preventable risks of CA (4).

Recommendations

In terms of primary prevention of CAs, the main recommendation is family planning. For unplanned pregnancies, it is difficult (nearly impossible) to make use of the recommendations that focus on eliminating possible risk factors. The percentage of planned pregnancies varies substantially among individual age and socio-economic groups – and, of course, across countries. Of EUROCAT countries, for instance, the percentage of planned pregnancies is high in the Netherlands (85%) and Switzerland (80%), medium in Italy (61%) and the United Kingdom (60%) and rather low in Portugal (54%) and Ireland (40% – 45%) (5).

Specific recommendations are then focused on targeted elimination of risk factors from the life of the mother (to be). These include known factors such as alcohol and smoking, but there are others to be mentioned: various infectious diseases (typically toxoplasmosis, herpetic infections, infections caused by human cytomegalovirus, rubella or syphilis), drugs, and, last but not least, the risk factors of a workplace (4).

In recent years attention has also been paid to the long-term pharmacotherapy of women with chronic diseases (such as epilepsy, arterial hypertension or diabetes mellitus). In this group, the long-term pharmacotherapy as well as possible mismanagement of the basic disease may pose a risk of CAs originating (6). Another growing problem is obesity of women in fertile age: as recent studies show, an increased risk of CAs is present in these cases due to correlations between obesity and a metabolic syndrome or diabetes mellitus (7).

Primary prevention of CA is currently high on the agenda of international organizations dealing with the epidemiology and prevalence of CAs. On a European level, the relevant organization is EUROCAT (8); globally it is ICBDSR (9). Various programs of primary prevention have been initiated worldwide, allowing professionals as well as the public to obtain relevant information. In the Czech Republic, a member state of both the mentioned organizations, the program "Think of me in time – before I get born", prepared in cooperation with the State Healthcare Institute, was launched in 2010 (4). Recommendations and promotional materials are available on the website of the Society of Medical Genetics of the Czech Medial Association of Jan Evangelista Purkyně (ČLS JEP) (www.slg.cz).

Folic Acid

Folic acid (acidum folicum, AF) is a water soluble vitamin of B group (5). Its role in preventing various types of CAs has been a topic for some time. The first mention of the possible connection between neural tube defects (NTD) and deficit of AF dates back to 1965 (10). Potentially positive effect of targeted supplementation of AF within prevention of NTD has been discussed from early 1980s (11,12). Positive effect of preventative use was then repeatedly confirmed in the early 1990s (e.g. 13,14).

Presently, most European states (in particular those associated within EUROCAT) have developed (un)official recommendations as regards periconception use of folic acid. There is no centralized approach, so individual recommendations differ slightly (***Tab. 1***); most often, a dosage of 0.4 mg of folic acid per day is recommended for mothers without an increased risk of NTD, and 4 mg for those with increased risk (family history, defects of metabolisms of folates or anti-epilepsy medication). As for the timing, the fortification is recommended at least 1 month before the conception and during the first three months of pregnancy. The definition of target population differs as well – most recommendations use the term "women planning pregnancy", or "women who wish to get pregnant"; less often a broader definition is used – "women who may get pregnant" (5). In the Czech Republic, a recommendation for supplementation of folic acid was developed within the mentioned project "Think of me in time – before I get born", which is consistent with the above. Specifically, a supplementation dosage of 0.4 mg of folic acid per day is recommended for women who could get pregnant or plan pregnancy, for at least one month before conceiving, while the increased intake of folic acid should be maintained at least for the first three months of pregnancy (15).

Outside Europe we see another phenomenon – official fortification of some basic food (mainly flour) with folic acid; this plays an important role in countries with a higher share of poorer socio-economic groups in the population, where usage of vitamin preparations containing AF would be unfeasible, financially or technically (17). ***Tab. 2*** shows 46 countries of North and South America, Asia, Africa, Australia or Oceania fortification with folic acid is presently obligatory.

Tab. 1 *List of European countries (associated within EROCAT) with existing recommendations as regards periconception use of folic acid (5,16)*

Country	Type of recommendation	Year of introduction	Recommendation
Austria	unofficial	1998	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy. Women who get pregnant without planning it should start supplementation without further delay, and continue until the end of the 8th week of pregnancy.
Belgium	unofficial	-	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy; 4 mg in the event of increased risk of NTD. AF to be taken 2-3 weeks before conceiving and for the first 3 months of pregnancy.
Croatia	unofficial	-	Most doctors recommend a daily dose of 0.4 mg of AF for all women planning pregnancy and 4 mg in the event of NTD in previous pregnancies. Usually it is recommended to start taking AF 4 weeks before conceiving and continue until the end of the 12th week of pregnancy.
Denmark	official	1997	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy; 5 mg for women with family history of NTD. AF to be taken from the start of planning pregnancy and for the first 3 months of pregnancy.
Finland	official	2004	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy and 4 mg for women with family history of NTD. AF to be taken from the discontinuation of the contraceptives / the last menstruation and continued until the end of the 12th week of pregnancy.
France	official	2000	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy and 5 mg in the event of NTD in previous pregnancies. It is recommended to start taking AF 4 weeks before conceiving and to continue until the end of the 8th week of pregnancy.
Germany	unofficial	1994	Recommended daily dose of AF is 0.4 mg for all women planning pregnancy and 4 mg in the event of NTD in previous pregnancies. It is recommended to start taking AF 4 weeks before conceiving and to continue for the 1st trimester of pregnancy.
Hungary	official	1996	All women planning pregnancy should be taking 0.4 mg AF daily for the entire non-conception period; the same dose should then be continued throughout the entire pregnancy.
Ireland	official	1993	Recommended daily dose of AF is 0.4 mg for all women who may get pregnant for the entire time before the possible pregnancy, and for the first 12 weeks of pregnancy.
Italy	official	2004	Recommended daily dose of AF is 0.4 mg for all women who plan to or may get pregnant. This dose has to be taken at least one month before conceiving and for the 1st trimester of pregnancy.
Malta	official	1994	Women who plan pregnancy should increase their daily supply of food rich in AF; no specific dosage is recommended.
Netherlands	official	1993	Recommended daily dose of AF is 0.5 mg for women planning pregnancy and 5 mg in the event of NTD in previous pregnancies; no specific recommendations are made as to the time of use.
Norway	official	1998	Recommended daily dose of AF is 0.4 mg for all women who plan to or may get pregnant; 4 mg for women with family history of NTD. AF to be taken for a month before conceiving and continued for the first 2-3 months of pregnancy.
Poland	official	1997	Women who plan to or may get pregnant should take 0.4 mg of AF daily; 4 mg in the event of NTD in previous pregnancies. No specific recommendations are made as to the time of use.
Portugal	official	1998	A recommended dose of AF is not specified. Supplementation is recommended for all women who may get pregnant, starting at least 2 months before discontinuing the contraceptives.

Country	Type of recommendation	Year of introduction	Recommendation
Slovenia	official	1998	Women who plan to or may get pregnant should take 0.4 mg of AF daily; 4 mg in the event of a family history of NTD. Ideally, AF supplementation should start in preconception period and continue for the first 12 weeks of pregnancy.
Spain	official	2001	Women who plan to get pregnant should take 0.4 mg of AF daily; 4 mg in the event of NTD in previous pregnancies. AF supplementation should be started before the planned pregnancy and continued for the first 3 months of pregnancy.
Sweden	official	1996	Women who plan to or may get pregnant should take 0.4 mg of AF daily; 4 mg in the event of a family history of NTD. AF supplementation should start in preconception period and continue until the end of the first trimester of pregnancy.
Switzerland	official	1996	All women in fertile age who may get pregnant should consume food rich in folates. Women who plan to get pregnant should take 0.4 mg of AF daily; 4-5 mg of AF per day is recommended in the event of NTD in previous pregnancies. AF supplementation should start 4 weeks before conceiving and continue for the first 12 weeks of pregnancy.
Ukraine	official	2002	Women who plan to get pregnant should take 0.4 mg of AF daily; AF supplementation should start 3 months before conceiving and continue for the first 16 weeks of pregnancy.
United Kingdom	official	1992	Women who plan to get pregnant should take 0.4 mg of AF daily; 5 mg of AF per day is recommended in the event of NTD in previous pregnancies. AF supplementation should start before conceiving and continue for the first 12 weeks of pregnancy.

The positive effect of country-wide fortification is documented for instance by a study carried out by a South American organization ECLAMC (Estudio Colaborativo Latino Americano de Malformaciones Congenitas), which proved the positive effect of fortification, for instance in reducing the frequency of spina bifida, anencephaly and encephalocele (18).

Discussion

Primary prevention of CA is a set of guidelines and recommendations, aiming to minimize the risk of occurrence of CAs. By its nature, primary prevention is not – and cannot be – 100% successful in preventing CAs from occurring. The first reason is that even by applying all available measure, we are only able to influence some – preventable – factors causing CAs; we are in effect unable to influence the non-preventable factors (such as new mutations). The second reason is the fact that most procedures within primary prevention have the character of guidelines or recommendations whose (non)observance is fully voluntary. Recommendations as regards family planning or change in lifestyle and diet will inevitably come to grief, as some people would be unwilling or unable, for various reasons, to observe them (5).

Tab. 2 *List of countries were fortification of food with folic acid is presently stipulated by law (16)*

Argentina	Dominican Republic	Iran	Puerto Rico
Australia	Ecuador	Iraq	Qatar
Bahrain	El Salvador	Ivory Coast	Saudi Arabia
Barbados	Fiji	Jamaica	South Africa
Belize	Ghana	Jordan	St Vincent
Bolivia	Grenada	Kuwait	Sudan
Brazil	Guadalupe	Mexico	Turkmenistan
Canada	Guatemala	Morocco	Uruguay
Chile	Guyana	New Zealand	USA
Columbia	Haiti	Nicaragua	Yemen
Costa Rica	Honduras	Oman	
Cuba	Indonesia	Paraguay	

Folic Acid is presently probably the only substance, which, if used in periconception period, may actively reduce the risk of at least one type of CA. The issue of general application of AF (even if just for women in fertile age) was repeatedly discussed also in terms of possible risks (a potentially higher risk of development of tumor diseases connected with significant external supply of AF was considered); however, there were also contrary opinions, mentioning other possible protective effects of long-term use of AF (reducing the risk of some types of tumors, for instance colorectal carcinoma). Neither of these extreme hypotheses was confirmed; the effect of long-term use of AF on the origination of tumors will thus have to be subject to further research (17,19).

Positive effects of AF supplementation in prevention of NTD are known. Relevant information on the effect of fortification of foodstuff with AF is currently available from North and South America, where a decrease in the incidence of certain types of NTD after introducing obligatory fortification was proved. Specifically, a 50% drop in the overall occurrence of spina bifida was observed after introducing the fortification in Canada (20); in South American countries, a drop of approximately 50% was observed in Chile and Argentina for the same defect (18). In European countries local studies are also available assessing the positive effect of supplementing the mother's food with AF preparations; an area-wide assessment of the effect is slightly more difficult here, as it is a case of voluntary recommendations rather than obligatory fortification of food (5).

A new approach to AF supplementation involves the de-

velopment of oral contraceptives also containing a recommended daily dose of the folate. These combined preparations work on the principle of increasing the plasma levels of AF in the course of their long-term use, which then ensures sufficient levels of AF at the point of sudden (whether planned or unplanned) discontinuation of their use, and conception. Studies are currently available from the United States of America (where this type of preparations has already gained a market license), confirming the effect of using these preparations on increasing plasma or erythrocyte folate levels (21,22).

Conclusion

Primary prevention of CAs has been gaining importance as part of comprehensive reproductive health care. It is based on the premise of planned parenting and targeted minimizing of harmful external factors. Supplementing the mother's food with AF is another important recommendation aiming to reduce the risk of NTD, both for the wide population of healthy pregnant women, and for women with an increased risk of NTD.

List of Abbreviations

AF	= acidum folicum
ECLAMC	= Estudio Colaborativo Latino Americano de Malformaciones Congénitas
EUROCAT	= European Concerted Action on Congenital Anomalies and Twins
ICBDSR	= International Clearinghouse for Birth Defects Surveillance and Research
NTD	= Neural Tube Defects
CA	= Congenital Anomalies

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