

Prevention of neural tube defects with folic acid: The Chinese experience

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Abstract

Neural tube defects (NTDs) are a group of congenital malformations of the central nervous system that are caused by the closure failure of the embryonic neural tube by the 28th day of conception. Anencephaly and spina bifida are the two major subtypes. Fetuses with anencephaly are often stillborn or electively aborted

due to prenatal diagnosis, or they die shortly after birth. Most infants with spina bifida are live-born and, with proper surgical treatment, can survive into adulthood. However, these children often have life-long physical disabilities. China has one of the highest prevalence of NTDs in the world. Inadequate dietary folate intake is believed to be the main cause of the cluster. Unlike many other countries that use staple fortification with folic acid as the public health strategy to prevent NTDs, the Chinese government provides all women who have a rural household registration and who plan to become pregnant with folic acid supplements, free of charge, through a nation-wide program started in 2009. Two to three years after the initiation of the program, the folic acid supplementation rate increased to 85% in the areas of the highest NTD prevalence. The mean plasma folate level of women during early and mid-pregnancy doubled the level before the program was introduced. However, most women began taking folic acid supplements when they knew that they were pregnant. This is too late for the protection of the embryonic neural tube. In a post-program survey of the women who reported folic acid supplementation, less than a quarter of the women began taking supplements prior to pregnancy, indicating that the remaining three quarters of the fetuses remained unprotected during the time of neural tube formation. Therefore, staple food fortification with folic acid should be considered as a priority in the prevention of NTDs.

Key words: Neural tube defects; Folic acid; Folate; Supplementation; Fortification

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Core tip: Neural tube defects are severe congenital malformations of the central nervous system. The prevalence of these defects in China is among the highest in the world. Low intake of dietary folate is to be blamed. The provision of free-of-charge folic

acid supplements to all women who live in rural areas and plan to become pregnant has been implemented since 2009. However, fortification of staple foods with folic acid has not been planned. It is time to consider fortification since many pregnancies are unplanned and therefore it is difficult for a woman to take folic acid supplements from before pregnancy.

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EMBRYONIC AND CLINICAL FEATURES OF NEURAL TUBE DEFECTS

Neural tube defects (NTDs) are a group of congenital malformations of the central nervous system that are caused by the failure of the embryonic neural tube to close by the 28th day of conception^[1,2]. Anencephaly and spina bifida are the two major subtypes of NTDs. A closure failure that occurs in the cranial region of the neural tube leads to anencephaly, which is characterized by the absence of the cranial vault and absent or markedly reduced cerebral hemispheres. Fetuses with anencephaly are often stillborn or electively aborted due to prenatal diagnosis, or they die shortly after birth. A closure defect occurring in the caudal region of the neural tube is referred to as spina bifida or meningomyelocele. This condition is characterized by bony defects in the spine through which the meninges and/or spinal cord tissue protrude to the body surface. Most infants with spina bifida are live-born and, with proper surgical treatment and management, can survive into adulthood. However, these children often have life-long physical disabilities, including leg paralysis, absence of control of urine and bowel, and learning difficulties. In addition, a large proportion of infants with spina bifida are complicated with hydrocephalus, which may lead to intellectual impairment and even premature death.

PREVALENCE OF NTD

NTDs are the second most common birth defect after congenital heart defects. It has been estimated that every year more than 320000 infants are born with NTDs worldwide^[3]. However, the prevalence of infants born with NTDs varies widely between countries and also within countries. In China, NTD epidemiology is characterized by a higher prevalence in the North than in the South and a higher prevalence in rural areas than in cities. A nationwide survey conducted in 1986-1987 showed an overall prevalence of 45.5 per 10000 births in the 15 northern provinces, compared with 11.3 per 10000 births in 12 Southern provinces^[4]. Of the northern provinces, Shanxi had the highest prevalence,

with 68.5 per 10000 births for males and 144 per 10000 births for females. During the same period, the prevalence of NTDs was 6 per 10000 births in the United States^[5]. Ireland is well known for its high prevalence of NTDs. East Ireland had a prevalence rate about 23 per 10000 births in 1986-1987^[6]. These data indicate that the prevalence of NTDs in Northern China is among the highest in the world. It has been estimated that around 100000 fetuses are affected annually in China. In recent years, the prevalence of NTDs in China has been declining consistently, but no national data are available to clarify how much of this trend is attributable to fewer NTD occurrences or to avoidance through pregnancy termination after prenatal diagnosis. This is because the national birth defects monitoring system includes only pregnancies of 28 wk' gestation or greater, thus not counting any pregnancies that are terminated before 28 wk' gestation. One study showed that more than two-thirds of NTD-affected pregnancies were terminated before 28 wk of gestation in the Shanxi rural population in early 2000s^[7]. This proportion is expected to be over 90% in urban populations. Surveillance data from 5 counties in Shanxi Province show that NTD prevalence declined from a peak of 120 per 10000 births in 2004 to 31.5 per 10000 births in 2014 (unpublished data). The latter remains much higher than the current prevalence of NTDs (5-7 per 10000 births) in the United States^[8].

DIETARY FOLATE INTAKE AND BLOOD FOLATE LEVELS OF WOMEN OF REPRODUCTIVE AGE

It has long been known that low blood folate during the periconceptual period is associated with an increased risk that a pregnancy will be affected by an NTD^[9]. Folate is the natural form of folic acid contained in food and in the body. Folic acid is the synthetic form that is used in supplements and fortified foods. Folate cannot be synthesized in the body and therefore can only be obtained from food. The typical diet of northern China is characterized by low amounts of fresh vegetables and fruits; this results in low blood folate. An investigation among women in Shanxi's rural population who were planning to become pregnant showed that the mean (\pm SD) and median (interquartile range) daily folate intake values were 114.3 ± 59.7 μ g/d and 102.8 (69.3-146.8) μ g/d, respectively. Virtually all (99%) of the women had an intake level below 320 μ g/d, the estimated average requirement for non-pregnant women, and only 1% and 7% of the women consumed 75% and 50%, respectively, of the recommended daily folate intake of 400 μ g for non-pregnant women^[10]. As a result of this low dietary folate intake, people living in the North have less than half the blood folate level of people living in the South. During early to mid-pregnancy, women living in the North had plasma and erythrocyte folate concentrations of 12.2 nmol/L and 440.0 nmol/L, respectively, compared to 33.5 nmol/L and 910.4 nmol/L,

respectively, for women living in the south^[11]. Low dietary folate intake and low blood folate concentration lead to a high risk of an NTD-affected pregnancy.

NATIONWIDE FOLIC ACID SUPPLEMENTATION PROGRAM

Although folate may be taken in naturally *via* the diet, folate intake from the diet alone cannot meet the needs of pregnant women and their growing fetuses. Folic acid supplements and consumption of folic acid-fortified cereals or staples are two alternatives to increase folate intake. In the late 1980s, a multicenter randomized controlled trial demonstrated that supplementation with 4 mg of daily folic acid during the periconceptional period could reduce the risk of NTD recurrence (*i.e.*, a subsequent NTD baby) by as much as 83%^[12]. A later randomized controlled trial conducted in Hungary showed that periconceptional supplementation with an 0.8 mg folic acid-containing multivitamin every day could prevent the first occurrence of NTDs^[13]. In the early 1990s, Peking University conducted a large-scale community interventional trial on the prevention of NTDs with folic acid with 247831 women of reproductive age, in collaboration with the Centers for Disease Control and Prevention of the United States. The results confirmed that periconceptional supplementation with only 0.4 mg of folic acid per day can reduce NTD risk by as much as 81%^[14]. However, science discoveries are not easy to translate into public health or clinical practice. For example, between 2002 and 2004, only 15% of pregnant women in Shanxi Province reported that they had ever taken folic acid supplements during the periconceptional period, and only one-third of these women took the supplements prior to pregnancy^[15]. To tackle this problem, the Chinese government launched a program that provides folic acid supplements, free of charge, to all women with a rural household registration who plan to become pregnant (estimated total number, 8 million) in 2009. The supplements are procured by provincial governments, but paid in total or in part by the central government. Local maternal health care workers are responsible for the distribution of the supplements. In 2011, the perinatal (28 gestational weeks to 4 wk of life) prevalence of NTDs decreased by 22.4% in rural areas compared to that in 2009^[16]. In 2011 and 2012, 2 to 3 years after the initiation of the supplementation program, the folic acid supplementation rate had increased to 85% in the areas of highest NTD prevalence^[17]. The mean plasma folate concentration of women during early and mid-pregnancy increased to 33.4 nmol/L (range, 18.7-58.4 nmol/L), double the level before the program was introduced^[18]. However, the proportion of women who began taking folic acid prior to pregnancy did not increase. In a post-program survey of the women who reported folic acid supplementation, 23.2% had begun taking supplements prior to pregnancy, compared to 27.3% in the pre-program survey in the

high NTD prevalence population^[17], indicating that many fetuses/embryos remained unprotected during the time of neural tube formation.

STAPLE FORTIFICATION WITH FOLIC ACID

The provision of folic acid supplements can be costly when manpower and the other logistical efforts involved in its distribution are taken into account. It is estimated that the Chinese central government needs 195 million RMB (about United States dollar 31 million) per year for supplement procurement. More important, many pregnancies are unplanned, meaning that supplementation with folic acid prior to pregnancy is impossible. On the other hand, staple fortification can supply folic acid "passively" to all women of reproductive age (and unintentionally to other segments of a population as well). Currently, about 80 countries have adopted or plan to implement staple fortification with folic acid^[19]. Reported NTD prevalence has been reduced by 28% in the United States^[8], by 46% in Canada^[20], and by 50% in Chile^[21] since fortification began. However, China has no plan to fortify staple foods in the foreseeable future. Perceived major barriers to the implementation of staple fortification include^[22]: (1) a lack of consensus in the scientific community; (2) the absence of a centralized production and distribution system for staples; (3) a lack of public awareness and acceptance; and (4) a lack of political will. The author hopes that these problems can be solved so that fortified flour and/or rice will become commercially available.

ROLE OF PEDIATRICIANS IN THE PREVENTION OF NTD

Since the recent change in China's family planning policy, more women wish to have a second baby. A proportion of these women are in their 30s or even 40s, meaning that they are at an increased risk of conceiving babies with down syndrome. In addition, advanced age is associated with a greater likelihood of obesity and diabetes, which are confirmed risk factors for NTD-affected pregnancies. This is an imminent challenge for the prevention of birth defects, including NTDs. In the battle to combat NTDs, physicians, including pediatricians, can play a critical role in every clinical encounter with women of reproductive age. For women who plan to have a second baby, pediatricians should advise them to take a 0.4-mg folic acid supplement daily beginning 3 mo prior to pregnancy or when there is a chance they may become pregnant. For women with a previous pregnancy affected by NTDs, it is recommended that they take 5 mg of folic acid daily, beginning from 3 mo before a pregnancy is planned. The ultimate goal is to protect each fetus from NTDs, which are preventable with folic acid.

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