News & Analysis

Medical News & Perspectives

Twenty Years After Folic Acid Fortification, FDA Ponders Expansion to Corn Masa Flour

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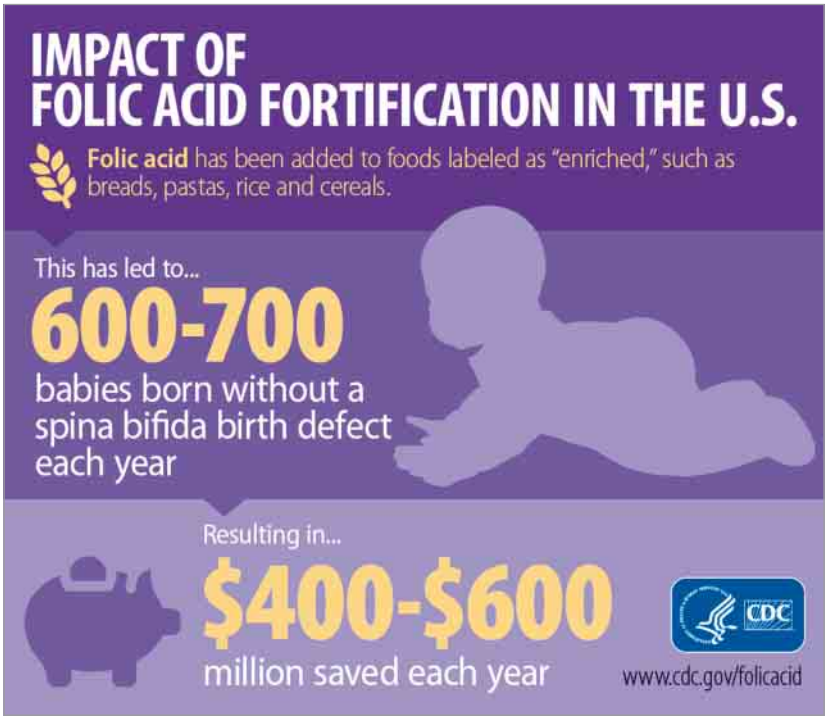
In 1993, James L. Mills, MD, MS, a senior investigator at the National Institute of Child Health and Human Development, attended a series of US Food and Drug Administration (FDA) subcommittee meetings. The subcommittee was considering whether to recommend fortifying cereal grain products with the B vitamin folic acid as a public health strategy to reduce the risk of infant neural tube defects. A year earlier, the US Department of Health and Human Services' Public Health Service (PHS) had recommended that all women of childbearing age consume 400 µg of folic acid daily to reduce the risk of having a child with spina bifida, anencephaly, or another neural tube defect (*MMWR Recomm Rep*. 1992;41[RR-14]:107). The PHS' recommendation was based, in part, on a landmark UK Medical Research Council clinical trial, which demonstrated that among women who had previously given birth to babies with neural tube defects, those who took 4 mg of folic acid supplements daily had a 72% reduced risk of having another baby with neural tube defects relative to those who did not take supplements (Wald N et al. *Lancet*. 1991;338[8760]:131-137). Despite the PHS' recommendation, committee members were cautious about moving forward with fortification, Mills recalled (http://1.usa.gov/1Rq9jDz).

"There was a lot of debate," said Mills. "[Fortification would] prevent hundreds of neural tube defects but expose 300 million people to folic acid… it was a very close vote."

One concern, he said, was that folic acid supplementation, which is also used to treat megaloblastic anemia, would mask the signs of B_{12} deficiency in older adults that could cause irreversible neurological damage; however, this turned out not to be the case, he said.

How folic acid reduces the risk of neural tube defects isn't completely understood, Mills explained, but the vitamin provides carbon atoms needed for DNA synthesis and plays a critical role in DNA methylation.

Ultimately, FDA officials crafted the final folic acid fortification regulations, which were published in early 1996 (*Fed Regist*. 1996;61[44]:8781-8797). By January 1, 1998, food manufacturers were required to add 140 µg of folic acid to every 100 g of cereal grain. The food of choice was cereal grains



Centers for Disease Control and Prevention

because they were already being fortified with other vitamins and minerals, and bread and other foods made from cereal grains are common food staples, said Cynthia Pellegrini, the March of Dimes senior vice president of public policy and government affairs. In addition, food manufacturers were permitted to add folic acid to infant formula, breakfast cereals, and medical foods, which are processed or formulated foods given as part of the treatment plan for people who are seriously ill or who have a chronic disease (http://1.usa.gov/1OJ8NMm).

One-Third Decrease in Spina Bifida

The effect of adding folic acid to enriched cereal grain products was striking. From October 1998 to December 1999, reported cases of spina bifida decreased 31% and reported cases of anencephaly decreased by 16%. The number of babies born with neural tube defects overall decreased from about 4000 infants in 1995-1996 to 3000 infants 4 years later (Centers for Disease Control and Prevention [CDC]. *MMWR Morb Mortal Wkly Rep*. 2004;53[17]:362-365). Fortification prevents an estimated 1300 neural tube defects each year in the United States (Williams J et al. *MMWR Morb Mortal Wkly Rep*. 2015;64[1]:1-5).

"Many put [folic acid fortification] on the list of the most effective public health interventions," said Krista Crider, PhD, a geneticist with the CDC's National Center on Birth Defects and Developmental Disabilities.

Fortifying cereal grains with folic acid not only prevented neural tube defects in about 1300 babies a year, but also "had a tremendous return on investment," noted Edward McCabe, MD, the March of Dimes chief medical officer. The FDA's action has saved $400 million to $600 million annually on care for children who otherwise would have been born with spina bifida (http://1.usa.gov/1KOurE3).

Hispanic Women at Risk

Even though fortifying cereals and grains has decreased the number of babies born with neural tube defects, CDC and March of Dimes experts said more work is needed to ensure that all women of childbearing age consume adequate folic acid by eating fortified foods and taking a daily supplement. Only 40% of women of childbearing age do so (CDC. *MMWR Morb Mortal Wkly Rep*. 2008;57[1]:5-8). The CDC and March of Dimes experts noted that adequate folic acid intake is particularly important for Hispanic women because they have a 21% higher risk of giving birth to a child with a neural tube defect than non-Hispanic white women (http://1.usa.gov/1S4pw3f). Crider explained that this may be partly due to Hispanic women being more likely to have a variant of the methylenetetrahydrofolate reductase (*MTHFR*) gene that results in reduced intracellular folate metabolism. In addition, they are less likely to consume recommended daily folic acid amounts: only 17% of Hispanic women report taking 400 µg or more of folic acid daily through fortified foods or supplements compared with 30% of non-Hispanic white women (Williams J et al. *MMWR Morb Mortal Wkly Rep*. 2015;64[1]:1-5).

Diet may play a large role. Hispanic adults tend to eat tortillas and other foods made with unfortified corn masa flour, rather than enriched cereal grain products, which is why the March of Dimes is lobbying for corn masa flour fortification, Crider noted. In 2012, the March of Dimes, American Academy of Pediatrics, National Council of La Raza, and Spina Bifida Association, along with 2 corn flour and food supplement manufacturers, petitioned the FDA to allow food manufacturers to voluntarily fortify corn masa flour with folic acid, said FDA spokesperson Megan McSeveney. At the FDA's request, last October the March of Dimes submitted data on folic acid's stability in corn masa flour, said Pellegrini. By April 15, the FDA will approve the request, deny it, or ask for additional information. Forty members of Congress sent a letter to the FDA in late February urging the agency to approve the request, Pellegrini said.

"The population with the highest risk hasn't had the benefit of folic acid fortification," McCabe said. "It would [have] a huge impact on the folic acid level in Hispanic women if we were able to fortify corn masa flour." ■

The JAMA Forum

Cultural Influences Reflected in Divergent US vs UK Human Embryo Research Policies

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In a first, the Human Fertilisation and Embryology Authority (HFEA) of the United Kingdom recently approved a research application to use a gene-editing tool on early human embryos (http://nyti.ms/219K7DR). The applicant, Kathy K. Niakan, PhD, a developmental biologist with the Francis Crick Institute in London, England, is seeking to define the molecular program of the earliest stages of human development.

The studies would use surplus embryos from in vitro fertilization treatments donated by consenting parties and would conclude at the embryonic blastocyst stage without transfer to a recipient uterus. Preliminary experiments to edit out select genes with an eye toward delineating their role in cell lineage fate specification—how the single cell of an embryo develops into different cell lines—may soon be under way.

Although nonhuman embryo research has proceeded unabated on both sides of the Atlantic, nonhuman models may not be the answer. Insights derived using nonhuman models, critical in their own right, must be extrapolated with caution to the human context but cannot fully substitute for research performed on human embryos.


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The dividends from human embryo research using genome editing could prove substantial. New insights into the relative inefficiency of human reproduction, the optimization of assisted