

Excess folic acid during pregnancy harms brain development of mice

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A UC Davis MIND Institute study of pregnant mice found that high amounts of folic acid during pregnancy harmed the brain development of embryos. Researchers say the findings indicate that more investigation is needed about the best recommended dosage for pregnant women.

"We believe there's a Goldilocks effect with folic acid. Too little is not good, too much is not good; you have to get it just right," said Ralph Green, UC Davis distinguished professor of pathology and medicine and a corresponding author of the study.

The research, published Sept. 30 in *Cerebral Cortex*, involved pregnant mice who were given either a normal amount of folic acid, 10 times the recommended amount, or none. The offspring of the mice that received the largest amount showed significant brain changes.

"It's not subtle. It's substantial," said Konstantinos Zarbalis, associate professor in the Department of Pathology and Laboratory Medicine and also a corresponding author of the research. "It makes a marked difference in [brain structure](#) if you take

very high amounts of folic acid."

Paradoxically, changes in the brain due to too much folic acid mimicked those associated with a deficiency of folic acid. "This, to me, was an even more important insight," said Zarbalis, who is also on the UC Davis MIND Institute faculty. He noted that in humans, research shows that impaired folate uptake into the brain can cause cerebral folate deficiency, a syndrome that is often associated with the development of autism.

Folic acid and pregnancy

Folic acid (the synthetic form of vitamin B9, or folate) supplementation is widely recommended for women of child-bearing age. It has been shown to substantially reduce the risk of neural tube defects, such as spina bifida, in children. Research, including studies at the MIND Institute, has also shown that prenatal vitamins that include folic acid have a protective effect against the development of autism and other disorders.

Green was on the panel with the National Academy of Sciences and the Institute of Medicine (now called the National Academy of Medicine) that determined the recommended daily intake of folic acid (400 mcg) and the maximum daily safe upper limit (1000 mcg). He was also on the Food and Drug Administration (FDA) panel that recommended adding folic acid to foods, which led to the fortification of all cereals and grains with folic acid mandated by the Federal Government in 1998.

"Addition of folic acid to the diet was a good thing, and I've supported fortification, but there is a 'best amount' of folic acid, and some people may be getting more than is optimal," said Green.

Women who have given birth to a child with neural tube defects or who have certain conditions like epilepsy and take anticonvulsants, have generally been advised to take much higher doses of folic

acid.

"In animal models, we have indications that very high amounts of folic acid can be harmful to [brain](#) development of the fetus, and the clinical community should take this indication seriously, to support research in this area to reevaluate the amount of folic [acid](#) that is optimal for [pregnant women](#)," said Zarbalis.

Zarbalis and Green suspect that the problem lies in the way [folic acid](#) is metabolized by the body and have plans to investigate the phenomenon further.

More information: Angelo Harlan De Crescenzo et al, Deficient or Excess Folic Acid Supply During Pregnancy Alter Cortical Neurodevelopment in Mouse Offspring, *Cerebral Cortex* (2020). DOI: [10.1093/cercor/bhaa248](https://doi.org/10.1093/cercor/bhaa248)

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